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The Nature and Origin of X Chromosome Aberrations in Turner's Syndrome

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A Cytogenetical and Clinical Study of 57 Patients

By JAN LINDSTEN

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THE NATURE AND ORIGIN OF X CHROMOSOME ABERRATIONS IN TURNER'S SYNDROME

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By

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STOCKHOLM
GÖTEBORG · UPPSALA

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THE NATURE AND ORIGIN OF X CHROMOSOME ABERRATIONS IN TURNER'S SYNDROME

A cytogenetical and clinical study of 57 patients

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som med vederbörligt tillstånd av Kanslern för rikets universitet för vinnande av medicine doktorsgrad kommer att offentligen försvaras på engelska språket i Karolinska sjukhusets aula onsdagen den 22 maj 1963 kl. 9 f.m.

Av

JAN LINDSTEN

med. och fil. kand.

UPPSALA 1963

Almqvist & Wiksells Boktryckeri AB

To Marianne

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INTRODUCTION

There are two main approaches to the study of X chromosome aberrations in man. In the first, all individuals with a certain X chromosome constitution within a population are selected for the analysis of some parameter, e.g. the significance of the aberration for the sexual development. In the second approach, patients with a particular clinical syndrome in which X chromosome aberrations are known to occur are investigated with respect to these aberrations. The former method has the obvious disadvantage of being extremely time-consuming, since a thorough analysis requires chromosome studies in all individuals within the chosen population, and this must be very large to include a substantial number of cases with the aberration in question. The latter method has one main disadvantage in that only subjects who have the chromosome aberrations together with a certain clinical picture are studied, while those who appear normal or nearly normal are eliminated by the selection. In the future the results of these two approaches may sometimes be found to coincide.

The author has preferred to use the second of the above methods, and a material consisting of 57 patients with Turner's syndrome was selected for this study. The selection of patients with Turner's syndrome for the study of aberrations of the X chromosome offers the following advantages: the clinical syndrome is, within certain limits, rather easily recognised after puberty; aberrations of the X chromosome occur almost invariably in Turner's syndrome; and, as became obvious in the course of the study, the aberrations are not only numerical but also of a structural nature.

Some attention has to be given to the definition of the clinical entity named Turner's syndrome. *Turner* (1938) in his original description considered the disease to be composed of the triad, infantilism (short stature and underdeveloped secondary sex characteristics), webbing of the neck and deformity of the elbow (cubitus valgus) appearing in female subjects. A considerable amount of information concerning the clinical picture has been obtained since this original description by *Turner*, and special attention has been given to the occurrence of abnormalities of the histology and function of the gonads and to symptoms which seemed directly connected with this. The term "ovarian agenesis" was introduced by *Olivet* (1923) and *Wilkins* & *Fleischmann* (1944) and referred to infantile women with short stature and aplasia of the ovaries. Reviews covering this devel-

opment were recently published by *Haddad* & *Wilkins* (1959), *Hauser* (1961) and *Polani* (1961, 1962).

The introduction of cytogenetical investigations in Turner's syndrome was followed by a large amount of literature dealing with the sex chromatin and chromosome abnormalities involved. In connection with this, and also with the introduction of new clinical findings in patients with this disease, it was not possible in many instances to maintain the old, rather simple definition of this clinical entity. Therefore, the definition of Turner's syndrome in recent literature varies, and has become somewhat vague. It seems too early at the present state of affairs to present a universal definition of Turner's syndrome or to delineate the different clinical entities connected with ovarian dysgenesis. The author has preferred to present the clinical findings on which he bases the diagnosis of Turner's syndrome as used in the present study.

The patients were selected primarily on clinical and not on cytogenetical criteria. Turner's syndrome as used here denotes a clinical entity composed of short stature, symptoms of ovarian dysgenesis, and a group of malformations other than short stature and ovarian dysgenesis.

Short stature is considered to be an obligatory sign, and only patients below or close to the lower 3σ limit for normal variation of height of Swedish women have been included.

Ovarian dysgenesis may, by definition, vary from total absence of functioning ovarian tissue (aplasia) to apparently normally functioning ovaries. Therefore, the sexual development may also show great variations, from severe underdevelopment to apparently normal secondary sex characteristics. Even menstruations over long periods of time have been described in such patients with ovarian dysgenesis (*Hoffenberg* & *Jackson* 1957, *Hutchings* 1959). One patient with Turner's syndrome and an XO sex chromosome constitution gave birth to a normal child (*Bahner et al.* 1960). Patients with Turner's syndrome who present definite symptoms of ovarian dysgenesis are clearly much more common than those with an almost normal development of the secondary sex characteristics. However, it cannot be excluded that this to some extent might be due to the fact that, in the latter group, the diagnosis is seldom made.

The types and number of *malformations* vary considerably in Turner's syndrome (see e.g. *Haddad* & *Wilkins* 1959, *Hauser* 1961). As shown by the present material, those originally stated by Turner, i.e. webbing of the neck and cubitus valgus, are not the most common ones. It should be emphasised in this connection that the judgment of malformations is prone to error, since it is so often totally subjective. In the present material some kind of malformation was always present.

From the above it is clear that each of the three units used by the

author to constitute the entity of Turner's syndrome may show great variations within a group of patients, and may approach normality. Therefore, all three groups of symptoms have always to be taken into consideration.

The question arises as to whether the presence of chromosome abnormalities should be considered as a prerequisite for the diagnosis of Turner's syndrome, i.e. as a fourth unit of the entity. Since these abnormalities form the central theme of the present work this question will now be discussed in some detail.

The introduction of cytogenetical studies in Turner's syndrome soon focused interest on the genetics of this disease. The application of methods for the study of sex chromatin (*Moore et al.* 1953, *Moore* & *Barr* 1955) and later also of drumsticks (*Tolksdorf et al.* 1955) in patients with various types of impaired sexual development, in 1954 led to the important discovery by *Polani et al.* and *Wilkins et al.* that patients with "ovarian agenesis" were sex chromatin negative. Studies on larger groups of such patients revealed that about 80 per cent of them were sex chromatin negative (e.g. *Nelson* 1956). This finding indicated that patients with "ovarian agenesis" did not have a normal female chromosome constitution. Such an opinion was supported by the finding of an increased frequency of colour-blindness among patients with "ovarian agenesis", and it was suggested that these patients were genetically males or, alternatively, had an XO sex chromosome constitution (*Polani et al.* 1956). Such an XO sex chromosome constitution was demonstrated in these patients for the first time in 1959 by *Ford et al.*, by the author (*Fraccaro et al.*) and by *Tjio et al.*

Other sex chromosome abnormalities, e.g. mosaicism, were soon observed in Turner's syndrome. The studies by *Danon* & *Sachs* in 1957, who found sex chromatin positive as well as negative areas in skin sections from two patients with "gonadal agenesis", suggested chromosome mosaicism, and this was confirmed by chromosome analyses in such patients by *Ford* (1961) and by the author (*Fraccaro et al.* 1960 *a*). Mosaicism was later observed rather frequently in patients with disturbed sexual development and, as will be shown in the present work, it is probably very common in cases with structurally abnormal X chromosomes. Some such structural aberrations are: the probable deletion of the long arm of the X chromosome (*Jacobs et al.* 1960), the presumptive iso-chromosome for its long arm (*Fraccaro et al.* 1960 *b*), and the probable deletion of its short arm (*Jacobs et al.* 1961). Of these, the two last types were found in patients with Turner's syndrome.

The various types of numerical and structural aberrations of the sex chromosome described in patients with Turner's syndrome, and found to be present almost invariably, are presented in Table 1. However, appar-

TABLE 1. *Different types of sex chromosome constitutions described in patients with Turner's syndrome, as diagnosed in the present work, and in other patients with probable ovarian dysgenesis.*

Diagnosis	Number of chromosomes	Sex chromosome constitution[a]	Authors
Turner's syndrome	45	XO	FORD *et al.* (1959), FRACCARO *et al.* (1959) and TJIO *et al.* (1959)
	46	XX	AUBERT (1962), DE LA CHAPELLE (1962) and ALMQVIST *et al.* (1963)
	46	XX_{DS}	JACOBS *et al.* (1961)
	46	XX_{I}	FRACCARO *et al.* (1960 *b*), ENGEL & FORBES (1961) and JACOBS *et al.* (1961)
	45/46	XO/XX	FORD (1961), FRACCARO *et al.* (1960 *a*) and SANDBERG *et al.* (1960)
	45/46	XO/XY	JACOBS *et al.* (1961) and MILLER *et al.* (1962)
	45/46	XO/XX_{DS}	ALMQVIST *et al.* (1963)
	45/46	XO/XX_{DL}	DE LA CHAPELLE (1962)
	45/46	XO/XX_{I}	BLANK *et al.* (1961) and LINDSTEN (1961)
	45/46	XO/Xf	FERRIER *et al.* (1962) and DE LA CHAPELLE (1962)
	45/47	XO/XXX	JACOBS *et al.* (1961)
	45/47	XO/XYY	JACOBS *et al.* (1961)
	45/46/47	XO/XX/XXX	HAYWARD & CAMERON (1961) and GRUMBACH & MORISHIMA (1962)
	45/46/47	$XO/XX_{R}/XX_{R}X_{R}$	LINDSTEN & TILLINGER (1962)
Other types of ovarian dysgenesis	46	XY	HARNDEN & STEWART (1959) and DE GROUCHY *et al.* (1960)
	46	XX	HAUSER *et al.* (1960) and JACOBS *et al.* (1961)
	46	XX_{DL}	JACOBS *et al.* (1960) and DE GROUCHY *et al.* (1961)
	47	XXX	JACOBS *et al.* (1959 *b*) and JOHNSTON *et al.* (1961)
	45/47	XO/XXX	JACOBS *et al.* (1960)
	45/47	XO/XYY	COOPER *et al.* (1962)
	45/46/47	XO/XX/XXX	CARR *et al.* (1962)

[a] X_{DS} = probable deletion of the short arm of X.
X_{I} = presumptive iso-chromosome for the long arm of X.
X_{DL} = probable deletion of the long arm of X.
f = fragment.
X_{R} = ring chromosome of X.

ently similar aberrations have been reported in pathological conditions other than Turner's syndrome: XO in phenotypic males with ambiguous external and internal genitalia and underdeveloped testicular tissue (*Bloise*

et al. 1960, *Atkins & Engel* 1962); XX in true hermaphrodites (e.g. *Hungerford et al.* 1959, *Harnden & Armstrong* 1959) and in male pseudohermaphrodism (*Shah et al.* 1961); XY in male pseudohermaphrodites and testicular feminization (e.g. *Jacobs et al.* 1959 *a*, *Lejeune et al.* 1960, *Lennox* 1961) and in a true hermaphrodite (*Eliachar et al.* 1962); XO/XY in true hermaphroditism (*Hirschhorn et al.* 1960) and in patients with ambiguous external and internal genitalia and underdeveloped gonads, mainly "streaks" and testis-like structures (e.g. *Blank et al.* 1960, *Conen et al.* 1961, *Willemse et al.* 1962); XXX mostly in mentally deficient women with primary or secondary amenorrhea and an otherwise apparently normal physical development (e.g. *Stewart & Sanderson* 1960, *Fraser et al.* 1960); and XX/XXX in a patient with Stein-Leventhal's disease (*de Grouchy et al.* 1961) and in a mentally deficient female (*Maclean et al.* 1962). However, it should be pointed out that usually only one tissue was analysed in the above patients, and therefore mosaicism might have been present in some more of them.

In this connection it should also be mentioned that patients with "male Turner's syndrome" (testicular germinal dysgenesis) have an apparently normal male chromosome constitution (*Fraccaro et al.* 1961, *Steiker et al.* 1961). Furthermore, structural aberrations of the X chromosome were described in other patients with disturbances in the sexual development: probable deletion of the long arm of X in Stein-Leventhal's disease (*de Grouchy et al.* 1961), in a patient with Klinefelter's syndrome (*Crawfurd* 1961) and in a male pseudohermaphrodite (*Miles et al.* 1962); an "enlarged X chromosome" in phenotypic males (*Oikawa & Blizzard* 1961, *Elves & Israëls* 1962); and chromosome fragments of unknown origin in patients with ambiguous external genitalia (*Vaharu et al.* 1961, *Fraccaro et al.* 1962).

From the above it is clear, firstly that patients with Turner's syndrome as defined here most often have sex chromosome aberrations but that these may be absent (Table 1), and secondly that the aberrations seen in Turner's syndrome may also occur in other clinical conditions. Therefore, at least at present, the author considers it somewhat premature to require specific chromosome abnormalities for the diagnosis of Turner's syndrome.

The aim of the present work was to study the nature and origin of aberrations of the X chromosome in patients with Turner's syndrome.

The different structural chromosome aberrations found had to be identified and verified. For this purpose morphological studies were used as well as measurements of the area and deoxyribonucleic acid (DNA) content of the sex chromatin and nuclei, and ^{3}H-thymidine labelling of the DNA synthesis of the chromosomes.

The origin of the single X chromosome in patients with an XO sex chromosome constitution and that of the structurally abnormal chromosomes were studied by the use of the sex-linked genes for deutan colour-blindness and the blood group Xg.

In addition, information has been obtained on the localisation of the deutan colour-blindness and Xg genes on the X chromosome.

Finally, it was decided to present a detailed analysis of the clinical picture of the present group of patients, and of the results of the vast amount of laboratory data. The purpose of this has been to provide material with special significance for clinical genetics for further studies in the future.

It should be mentioned that this presentation includes hitherto unpublished data as well as findings recently reported by the author.

MATERIAL AND METHODS

Material

The case material comprises 57 patients who, according to the definition given on p. 10, were considered to have Turner's syndrome. They are presented in detail in the Case reports and in the tables and figures of the Appendix. Much of the data given in the Appendix will not be discussed in detail. However, the author considered it important to include this data in order to give an account, as complete as possible, of the case material and also to make it available for future studies. The case material has been divided into the following groups according to the sex chromosome constitution: patients with an XO constitution (Nos. 1–35), with a presumptive iso-chromosome for the long arm of X (Nos. 36–46), with an XO/XX mosaicism (Nos. 47–53) and with other constitutions (Nos. 54–57). The cytogenetic criteria behind this division will be discussed on pp. 20. Within each group the order of the patients was determined by the age at the last examination.

All patients, except Nos. 14 and 46, were born in Sweden and their parents and grandparents were also born here. Their antecedents were not followed further. The present case material might not be representative of Turner's syndrome as a whole, since the most severely malformed individuals with this disease may die at an early age or be referred to institutions for the mentally retarded and thus escape diagnosis. Furthermore, patients who have Turner's syndrome but whose height is close to the lower normal limit, and/or who have normal menstrual cycles, most probably remain undiagnosed.

Almost all the subjects were between the ages of 12 and 40 years when they first came to the clinic or were referred to us by other physicians because of short stature and/or amenorrhea. Exceptions are Cases 1, 2 and 3 who were studied before one year of age because of localised oedema of hands, feet and lower legs, and were found to have an XO sex chromosome constitution. Case 4 was diagnosed at the age of seven when she consulted a physician because of short stature.

The ages of the patients at the last examination were seven and a half months to 42 years. The majority, 49 out of 57, were between 16 and 30, and 40 were between 16 and 25 years of age.

During the last two years almost all the patients had been hospitalized at least once. The exceptions were some of the previously described cases who either could not be reached again or refused further hospitalization. However, it was considered worthwhile to include them in the case material, since they were among the first patients with Turner's syndrome, in whom cytogenetical aberrations were described. References to earlier published cases are found at the beginning of each case report.

A standard program of investigations was made and followed as carefully as possible. Due to the reasons given above, all patients have missed part of the program. There is thus a lack of information on certain points.

Birth charts and charts from earlier hospitalizations were collected. Observations regarding body height at different ages were obtained from school health cards. Many of the patients had been treated for various periods of time. The treatment generally used was cyclical administration of oestrogens. One cycle consisted of three weeks with oestrogens followed by one week without. If any other treatment was used this is pointed out in the case reports.

Methods[1]

Cytological methods

Drumsticks were studied in cells from blood smears stained with May Grünewald-Giemsa according to *Davidson & Smith* (1954). In each case 500 neutrophil leucocytes were scored.

Sex chromatin was investigated in skin sections. Some of these were stained with the Feulgen method, others with haematoxylin-eosin or van Gieson. Only a qualitative diagnosis was made. This was also the case when the sex chromatin was studied according to the method of *Fraccaro & Lindsten* (1959) in cells from skin or bone marrow biopsies grown in long-term cultures. Sex chromatin was studied quantitatively and qualitatively

[1] Measurements of the area and DNA content of the sex chromatin and nuclei were performed in collaboration with Drs. *H. P. Klinger,* Basel, and *M. Fraccaro* and *I. Barrai,* Pavia. Dr. *H. P. Klinger,* Basel, also cultured the cells from skin biopsies used for area and DNA measurements. ^{3}H-thymidine labelling was performed in collaboration with Dr. *S. Muldal,* Manchester, and Dr. *Janet Rowley,* Chicago. The gynaecological investigations were performed by Dr. *K.-G. Tillinger,* the cardiological investigations by Dr. *Inga Rune,* the anomaloscopic investigations of the colour-blind patients by Dr. *I. Rendal,* the odontological examinations by Dr. *R. Filipsson,* and the intelligence tests were performed and interpreted by Prof. *B. Cronholm* and *L. Molander,* B.A., all from Stockholm. All radiological investigations were interpreted by Dr. *N. Lindvall,* Stockholm. Blood group and serum protein group analyses were performed by the Blood Group Serology Department, State Laboratory of Forensic Chemistry, Stockholm (head Prof. *B. Broman*). The Xg blood group analysis was made by Drs. *R. Race* and *Ruth Sanger,* London. Dr. *J. Jackson,* Uppsala, carried out the examinations for micronuclei in mononuclear cells in blood smears from Case 55. Audiometric analyses were intepreted by Dr. *E. Wedenberg,* Stockholm. Assays of total gonadotrophins and of biologically and chemically determined oestrogens in urine were performed by Dr. *E. Diczfalusy,* Stockholm. Dr. *S. Almqvist,* Stockholm, performed the assays of serum sulphation factor activity.

in cells from buccal mucosa smears, on which the staining technique described by *Klinger* & *Ludwig* (1957) was used. Only sex chromatin bodies at the nuclear membrane were counted for quantitative estimations.

The following method was used to measure the area of sex chromatin and nuclei in Feulgen stained cells of buccal mucosa smears and from long-term skin cultures. All cells were photographed in the same microscope (Zeiss photomicroscope), and all films (Duplopan) developed under identical conditions. The negatives were then projected to a constant magnification (× 11,000), and the cells traced on the screen with a pencil. The areas of the nuclei and sex chromatin bodies were calculated with a planimeter.

The same preparations were also used for measurements of the DNA content of the sex chromatin and nuclei. These measurements were performed as described by *Klinger* & *Schwarzacher* (1960), and with the same instrument.

Cultures of leucocytes from peripheral blood were prepared and processed according to the method of *Moorhead et al.* (1960). Some minor modifications without general implication were, however, made by the author. Chromosome preparations were obtained with the air-drying technique, and the preparations were stained in 60 per cent acetic-orcein.

When several blood specimens were taken and processed, there was an interval of one to six months between them. In one case, No. 6, the short-term incubation method for bone marrow biopsies according to *Tjio* & *Whang* (1962) was used. Long-term cultures of cells from bone marrow and skin biopsies were prepared by the method of *Fraccaro et al.* (1960 *c*). The repeated bone marrow biopsies in Cases 40 and 44 were taken at intervals of about one month. The skin biopsies used for studies of the size and DNA content of the sex chromatin mentioned above, were cultured and also prepared for chromosome investigations according to the method of *Hsu* & *Kellogg* (1960) with some modifications introduced by *H. Klinger* (unpublished). These preparations were stained with a slightly modified Giemsa stain. In Cases 38 and 55, there was more than six months' interval between the repeated skin biopsies. Cells grown in long-term cultures were generally studied before the second or third transplantation *in vitro*, i.e. before three to six weeks after the biopsies were taken.

Chromosome counts and primary analyses of the karyotypes were made in a Zeiss Photomicroscope. Phase contrast was used for the acetic-orcein stained slides, in other instances an ordinary light microscope was used throughout the study. A second analysis of the karyotypes was made on enlarged microphotographic copies. The film used was ADOX KB 14. *The Denver system for classification of human mitotic chromosomes* was used throughout this work.

Chromosome measurements were performed according to *Fraccaro* & *Lindsten* (1960 *a*). The labelling of cells with ^{3}H-thymidine and the statistical evaluation of grain scores over chromosomes were carried out as described by *Gilbert et al.* (1962).

Clinical studies

An interview with the patient, and in most cases with one of the parents, was the basis for the pedigree analyses. Special attention was given to twins, sex ratios, abortions and conditions known to be connected with chromosome abnormalities.

All patients were examined with special regard to malformations and signs of ovarian insufficiency. Routine gynaecological and cardiological investigations, including electrocardiograms and often phonocardiograms, were performed. Data regarding normal variations of body height in healthy Swedish females of various ages were obtained from *Broman et al.* (1942) and *Karlberg* & *Perman* (1959).

Colour vision was studied with the 15th edition of the Ishihara charts. In patients with colour-blindness according to these charts, anomaloscopic examinations were performed. Relatives were only studied with the Ishihara charts, except for Case 38 where all relevant individuals were also examined with the anomaloscope.

The height of the palate arch was measured on plaster casts according to the method described by *Lundström* (1948).

The level of intelligence was measured with a Swedish modification of the Wechsel-Bellevue scale (CVB) (*Husén* 1956), and with another scale (SRB) composed of three different subtests: a synonym test of multiple choice type, a "reasoning" test and a block test of Koh's type (*Dureman* & *Sälde* 1959).

Detailed radiological investigations were made of the heart, kidneys and skeleton. The evaluation of the whole material was made by the same radiologist. The assessment of skeletal age was made according to *Schinz et al.* (1952).

Blood group and serum protein group analyses were performed in most cases, and the nomenclature used has been described by *Race* & *Sanger* (1962) and *Hirschfeld* (1962). The Xg blood group (*Mann et al.* 1962) was investigated in families where blood could be obtained from both parents.

Audiometric analyses with a tone audiometer (Amplivox) were carried out. The following criteria were used for the diagnosis of hearing impairment: a maximum impairment of at least 20 decibels (dB), impairment below 8000 cycles/second (c/s) and broader than one octave. The children were tested according to *Wedenberg* (1956). The nomenclature used will be described by *Wedenberg* (in preparation).

A saturated solution of phenylthiocarbamide was used to test the ability to taste this drug.

Sodium, potassium and calcium levels in serum were determined with flame photometers, the two former with an Eppendorf flame photometer, and the latter with a Zeiss flame spectrophotometer. Bicarbonate in serum was determined according to *van Slyke* (1922) and chlorides in serum according to *Zall et al.* (1956). Serum protein-bound iodine (PBI) was determined according to *Barker et al.* (1951), plasma inorganic phosphate according to *Gomori* (1941–42), serum acid phosphatase according to *Kaplan & Narahara* (1953), serum alkaline phosphatase according to a combination of the methods described by *Powell & Smith* (1954) and *Kind & King* (1954), serum cholesterol according to *Pearson et al.* (1952), urinary 17-ketosteroids according to *Vestergaard* (1951), urinary 17 ketogenic steroids according to *Norymberski et al.* (1953) as modified by *Appleby et al.* (1955), total urinary gonadotrophins according to *Klinefelter et al.* (1943), biological assays of urinary oestrogens according to *Brown* (1955) as modified by *Diczfalusy & Westman* (1956), and chemical determinations of oestrone, 17β-oestradiol and oestriol according to *Brown et al.* (1957). The intravenous glucose tolerance tests were performed according to *Ikkos & Luft* (1957). Serum sulphation factor activity (SF) was determined according to *Almqvist* (1961). Radio-iodine tests were performed according to *Einhorn* (1958). Total serumproteins were determined in a Technicon Autoanalyser according to the Biuret method, and paper electrophoresis of the serum was carried out. The amino acid pattern and the indoles in urine were determined in a few cases both with paper chromatography according to *Redfield* (1953) with some modifications and according to *Jepson* (1955), respectively. The amino acid pattern in urine was also investigated with the high voltage electrophoresis method of *Michl* (1958).

Some routine tests on blood (haemoglobin, number of red and white blood cells and differential counts) and on urine (albumin, glucose, sediment and calcium excretion), were performed in most cases. Only pathological findings are mentioned in the case reports, and the results of these routine tests are not included in any of the tables.

RESULTS

Cytological studies

Analyses of somatic chromosomes, sex chromatin and drumsticks

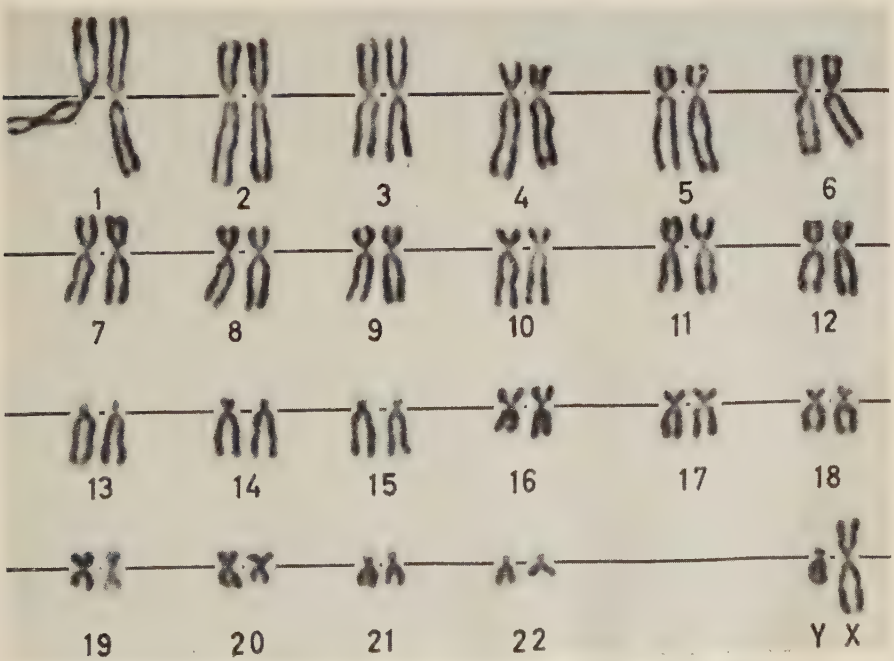
General

As mentioned on p. 17 *the Denver system for classification of human mitotic chromosomes* has been used in this work. A representative metaphase and karyotype from a normal male and female are shown in Figs. 1 and 2 in order to illustrate the classification. Thus, the autosomes were paired visually according to size and position of the centromere, and numbered according to decreasing length. The X chromosome could not be identified with certainty on morphological criteria. In spite of this, a chromosome meeting the criteria for a presumptive X, as well as structurally abnormal chromosomes believed to be derived from X, were placed separately in each karyotype in order to demonstrate clearly the various abnormalities. These abnormalities could not have been diagnosed without parallel studies of sex chromatin and drumsticks, and therefore, these latter will be discussed together with the chromosome analysis. The diagnoses of the different aberrations were further strengthened by the study of the area and DNA content of the sex chromatin and nuclei (p. 38 and pp. 35) and by ^{3}H-thymidine labelling of the DNA synthesis (pp. 39) in cells from these patients.

The various methods for chromosome studies used in the present work, i.e. the air-drying and squash techniques, gave somewhat different results. These differences were in the degree of deviation from the modal number of chromosomes, towards both lower and higher chromosome numbers. Cells with chromosome numbers deviating from the modal number were always analysed in detail in order to establish whether there was a consistency in the deviation, i.e. whether mosaicism could be suspected. In such a case, a larger number of cells was counted and, if possible, another tissue specimen analysed.

The squash technique, mainly used during the early phase of this study, gave more extreme deviations from the modal number, while the deviations were comparatively small when air-drying was used. When some of

Fig. 1. (*a*) Mitotic metaphase in a leucocyte from a culture of peripheral blood. 46 chromosomes. Acetic orcein stain. Phase contrast. × 1500.



(*b*) The chromosomes of Fig. 1 *a* arranged according to size and position of the centromere. Normal male karyotype. × 2200.

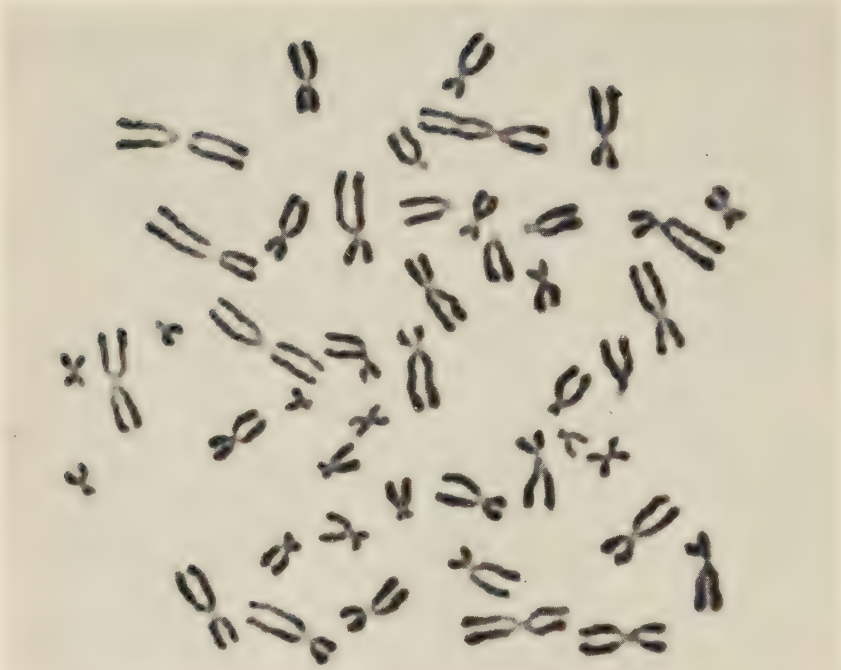


Fig. 2. (*a*) Mitotic metaphase in a leucocyte from a culture of peripheral blood. 46 chromosomes. Acetic orcein stain. Phase contrast. × 2300.

(*b*) The chromosome of Fig. 2 *a* arranged according to size and position of the centromere. Normal female karyotype. × 2700.

the earlier patients were later re-examined by the use of the latter technique the previous interpretations could always be confirmed.

The frequency of deviations towards higher chromosome numbers was always less than that towards lower numbers, the latter depending to a larger extent on the selection of cells for analysis. Table 13 shows whether the deviations were constant, i.e. if they were interpreted as being due to mosaicism. The magnitude of the deviation with the air-drying technique was 7.3 per cent of all 3087 cells counted from peripheral blood cultures from the XO cases in the present material. With the same technique, extra chromosomes were only found in one or two cells in Cases 28, 32 and 55. In spite of this, Cases 28 and 32 were not interpreted as mosaics, while Case 55 was an otherwise clear mosaic and will be discussed on pp. 29.

Polyploid cells and endoreduplications were present in varying frequencies, and association of acrocentric chromosomes, satellites and secondary constrictions were frequently observed. In no case were the satellites found to be of an unusually large size. These observations will not be discussed further in the present work.

It might be questioned whether the chromosome constitution obtained by studies of cells cultured *in vitro* reflects that of the same tissue *in vivo*. This is of special importance for the diagnosis of mosaicism. The following findings are in favour of such a view.

In one of the patients (No. 6), cells from short-term incubation of a bone marrow biopsy and from cultures of peripheral blood gave identical results. Furthermore, most of the cells in cultures of peripheral blood are probably in their first or not more than in their second mitosis (*Bender & Prescott* 1962). There were in the present material no apparent differences in mitotic activity between cells with different karyotypes. When several blood cultures were made from the same patient (e.g. Case 55) the proportion of the different cell types was fairly constant from time to time. Finally, cells from long-term cultures still had 45 chromosomes and an XO sex chromosome constitution after 15 serial transplantations during four months (Case 19) (*Fraccaro et al.* 1960 *c*).

On the other hand, a ring chromosome (Case 55) seemed to be eliminated after two to four transplantations *in vitro*. The preferential loss is probably due to the structural abnormalities which a ring undergoes at mitosis (see pp. 30). Presumptive iso-chromosomes did not seem to be eliminated, but long-term cultures were only followed for one month and four serial transplantations. It should also be mentioned that the proportion of the different cell types changed after the third transplantation in Case 48 (*Fraccaro et al.* 1960 *a*).

In conclusion, short-term incubation of cells from the bone marrow will probably give the most valid results, and there are probably no great

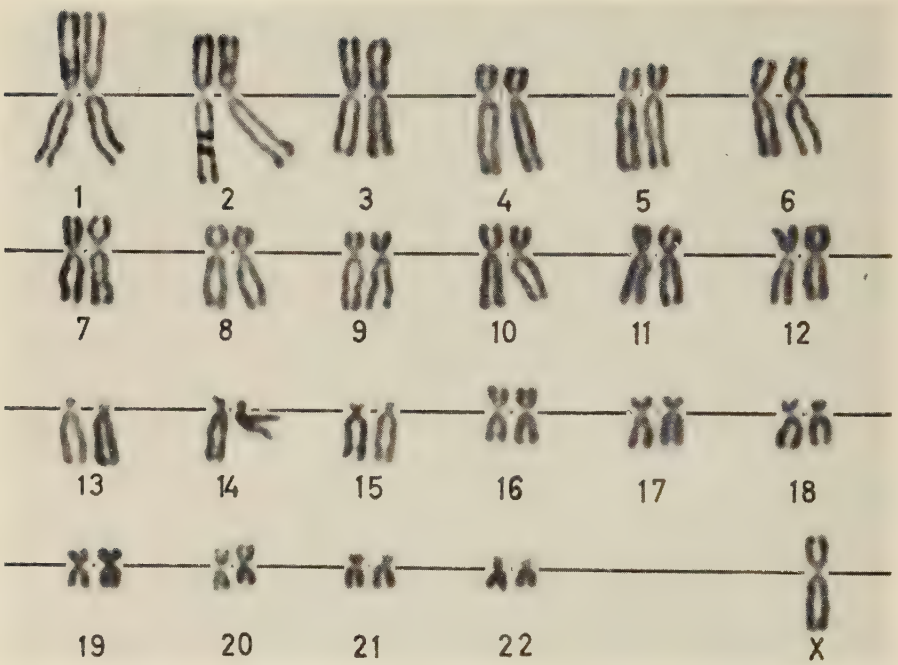
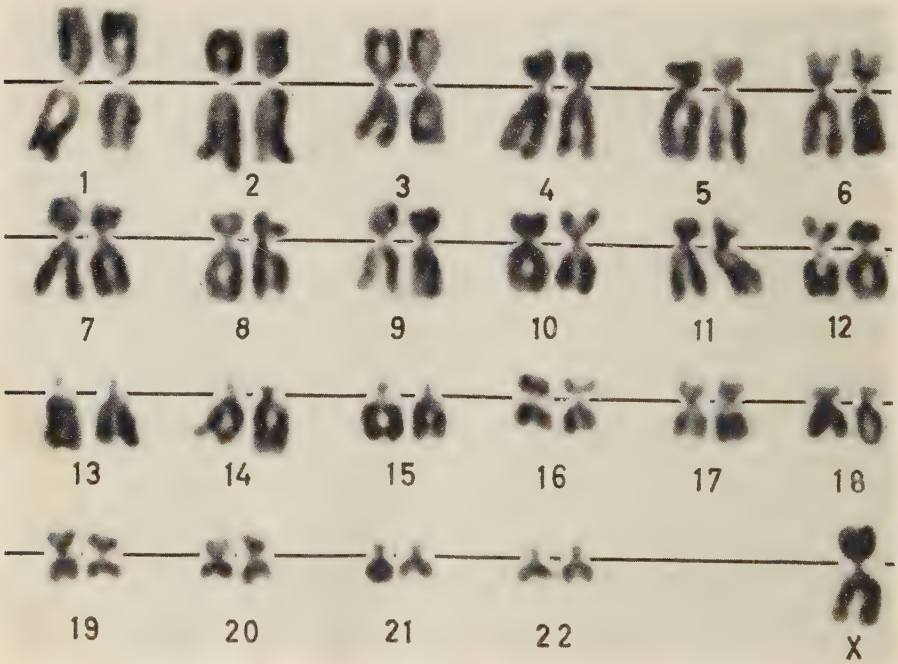
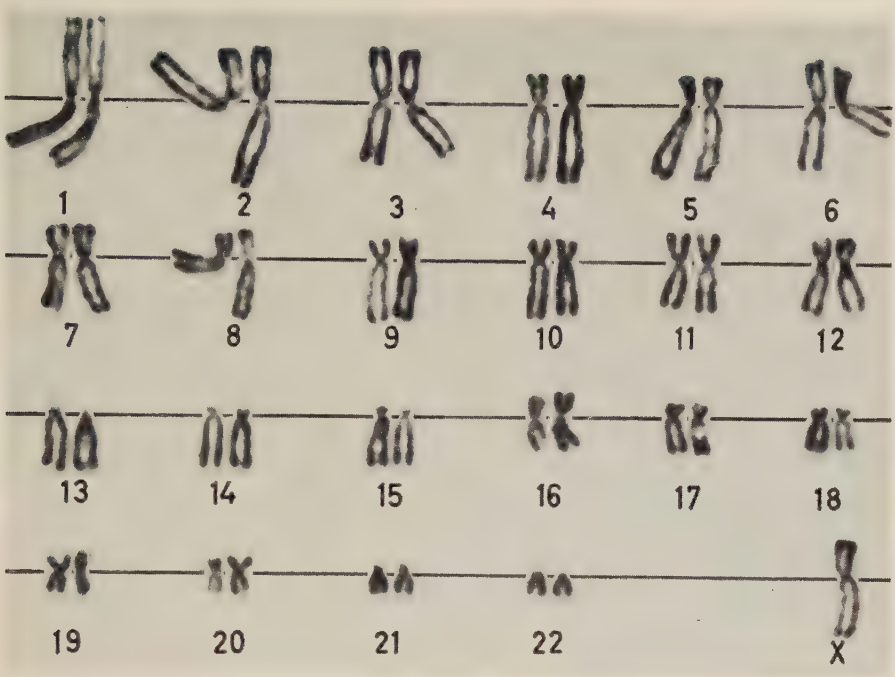


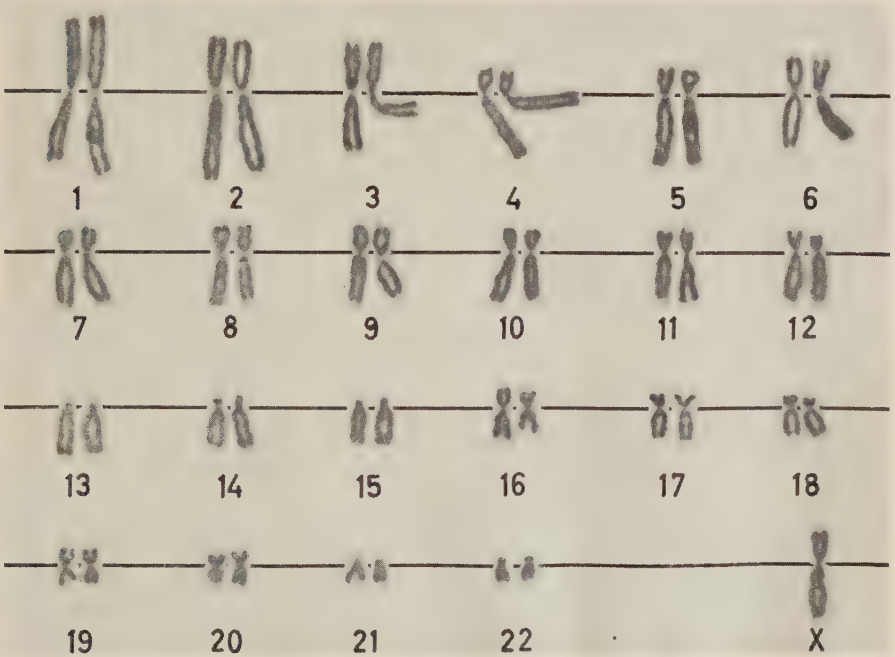
Fig. 3. (*a*) Karyotype from a mitotic leucocyte from Case 23. 45 chromosomes and an XO sex chromosome constitution. Acetic orcein stain. Phase contrast. × 2100.



(*b*) Karyotype from a mitotic bone marrow cell (short-term incubation) from Case 6. 45 chromosomes and an XO sex chromosome constitution. Acetic orcein stain. Phase contrast. × 2500.



(*c*) Karyotype from a mitotic bone marrow cell (long-term culture) from Case 28. 45 chromosomes and an XO sex chromosome constitution. Acetic orcein stain. Phase contrast. × 2700.



(*d*) Karyotype from a mitotic skin cell from Case 42. 45 chromosomes and an XO sex chromosome constitution. Giemsa stain. Ordinary light. × 2100.

differences in selection of various cell types in blood cultures. Selection might, on the other hand, play a role in long-term cultures, at least in cases with mosaicism. This was especially noted for cells with a ring chromosome of X.

The presence of mosaicism has important practical consequences. It complicates for example the interpretation of results from studies with marker genes. The diagnosis of chromosomal mosaics depends on the number of cells and tissues analysed and probably also on the culture methods used. In the present material two tissues were analysed in about half of the cases. It is likely that investigations of several tissues from all the patients would have revealed mosaicism in some additional cases.

The clinical material examined in this study has been divided into groups according to the sex chromosome constitution of the propositi. The results will be discussed under the following headings: The XO sex chromosome constitution; Presumptive iso-chromosomes for the long arm of X; XO/XX mosaicism; Ring chromosome of X; and Other chromosome constitutions. Detailed results of chromosome counts and of drumsticks and sex chromatin are given in Table 13.

The XO sex chromosome constitution

Thirty-five patients (Cases 1–35) were found to have cells generally with 45 chromosomes and one chromosome missing in the group 6-12-X. The patients were consistently sex chromatin negative in skin sections (eight cases), buccal mucosa smears (32 cases) and in cells grown in long-term cultures (16 cases). No drumsticks were found in the neutrophil leucocytes. Representative karyotypes are shown in Fig. 3.

As shown in Table 13 the cells with chromosome numbers deviating from 45 showed no constant karyotypes. In only two such instances, Cases 28 and 32, a chromosome number above 45 was found in cells from peripheral blood cultures, but only in *one* cell from each of the patients out of 109 and 75 cells studied respectively. It could not be decided whether these findings were due to technical errors or represented true mosaicism, although the former explanation seems most probable.

In this connection it should be mentioned that sex chromatin in buccal mucosa smears was found to be normal in the parents and sibs of the colour-blind XO patients (Nos. 18 and 30). In addition, the karyotypes of the parents of two of the patients of the XO group (Nos. 6 and 9) were studied and found to be normal. These findings, together with the fact that the parents were obviously healthy people, speak in favour of the opinion that parents of XO patients generally do not have sex chromosome abnormalities.

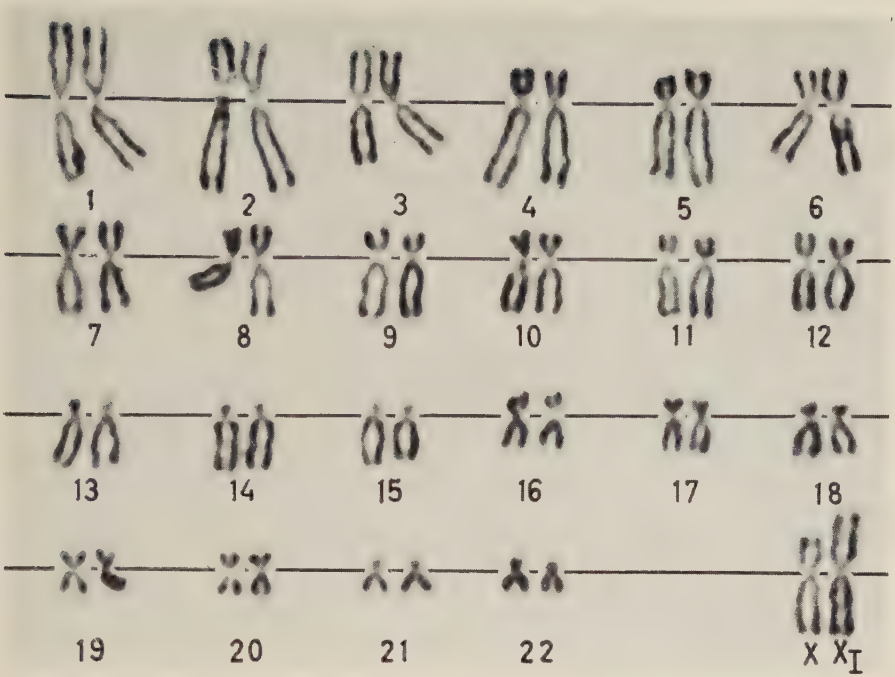


Fig. 4. Karyotype from a mitotic leucocyte from Case 43. 46 chromosomes with an apparently normal X chromosome and one presumptive iso-chromosome for the long arm of X (X_I). Acetic orcein stain. Phase contrast. × 2400.

Presumptive iso-chromosomes for the long arm of X

Eleven patients (Cases 36–46) were found to have cells with 46 chromosomes and an abnormal karyotype consisting of an extra chromosome, identical with pair No. 3, and one missing chromosome in the group 6-12-X (Fig. 4). Measurements of arm ratios and relative chromosome lengths in karyotypes with this abnormality (*Lindsten et al.* 1963 *b*) showed that this extra chromosome was indistinguishable from chromosome No. 3, and was double the size of the long arm of the normal X chromosome.

A sex chromatin positive pattern was found in cells of buccal mucosa smears from all the 11 patients and in skin sections which were investigated in seven of these, as well as in bone marrow and skin cells grown in long-term cultures, which were studied in six of the patients. Furthermore, drumsticks were found in a proportion of the neutrophil leucocytes in 10 of the cases. On the basis of these findings the extra chromosome was interpreted as a presumptive iso-chromosome for the long arm of X (X_I). Further evidence for the iso-chromosome hypothesis was obtained from ^{3}H-thymidine labelling (pp. 39).

In only two of the 11 patients (Cases 36 and 44) no evidence of mo-

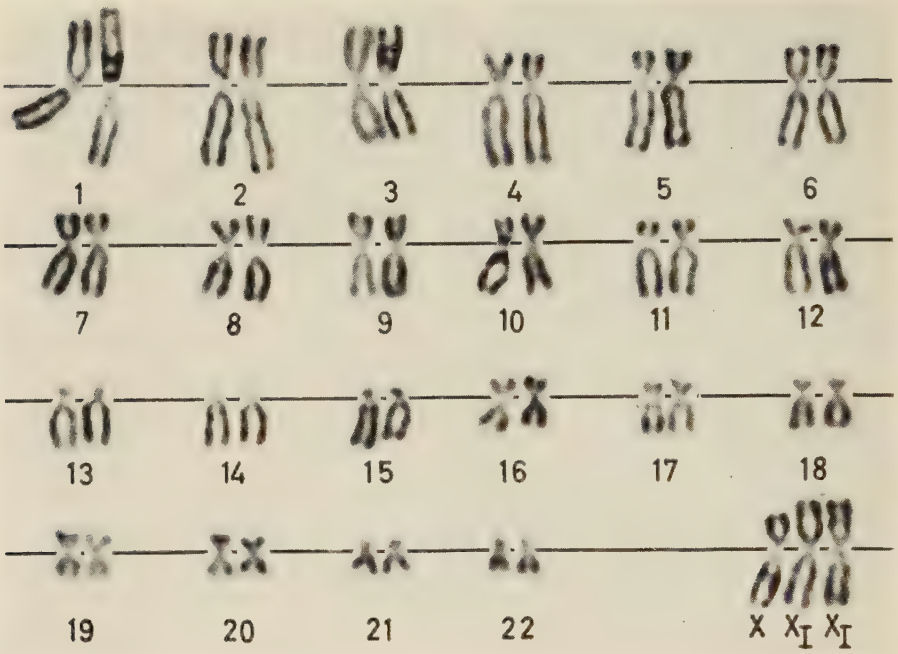


Fig. 5. Karyotype from a mitotic leucocyte from Case 43. 47 chromosomes with one apparently normal X chromosome and two presumptive iso-chromosomes for the long arm of X (X_I). Acetic orcein stain. Phase contrast. × 2400.

saicism was found; two and three different tissues, respectively, were analysed in these two cases. Apart from cells with 46 chromosomes and a presumptive iso-chromosome, the nine patients with mosaicism had cells with 45 chromosomes and one chromosome missing in the group 6-12-X. The latter cells were interpreted as having an XO sex chromosome constitution. In addition, one of the nine patients with mosaicism (No. 43) also had some cells with 47 chromosomes containing two presumptive iso-chromosomes and one apparently normal X chromosome (Fig. 5).

As seen in Table 13, the proportion of the above cell types varied in the nine patients, and there was also a difference in this respect between tissues from the same patient. However, when two blood specimens were cultivated they were generally in good agreement. On the other hand, in one case (No. 38) two skin biopsies showed differences in the proportions of the cell types.

The percentage of sex chromatin positive cells in buccal mucosa smears showed some variations between the 11 patients. It is noteworthy also that the proportion of sex chromatin positive cells varied considerably between different samples of buccal mucosa in Case 40 (*Lindsten et al.* 1963 *b*), and that there was a normal percentage of positive cells in Case 41 in

spite of the high proportion of XO cells in the skin cultures. All these findings indicate that the mosaicism, i.e. the proportion of the different cell types, varied in the present nine patients. A variation between patients in the number of drumsticks could also be demonstrated in the neutrophils. A direct comparison between the number of drumsticks and the proportion of cells with more than one normal X chromosome has not been made since it is probably the small lymphocytes and not the neutrophil leucocytes that are actively dividing in the blood cultures and are used for chromosome counting (*Nowell* 1960, *Carstairs* 1962).

In some cells from these patients with iso-chromosomes the sex chromatin body appeared unusually large. Objective measurements of its area and DNA content were therefore taken, and the results are presented on pp. 35.

Since the structurally abnormal chromosome of the type described here could be the result of a translocation, it was considered necessary to examine the karyotypes of parents of the patients. The parents and sibs of patients Nos. 40, 41 and 44 were investigated in this respect, and were all found to be normal. In addition, the cells in the buccal mucosa smears were normal in the parents and the sibs of Case 38, where colour-blindness was found in the family (pp. 42).

XO/XX mosaicism

This type of mosaicism was found in seven cases (Nos. 47–53) who were consistently sex chromatin positive in cells of buccal mucosa smears. Different proportions of cells with 46 chromosomes and an apparently normal female karyotype on one hand, and cells with 45 chromosomes and an XO sex chromosome constitution as described above on the other, were found. In two of the patients (Nos. 47 and 51) there were no, or very few cells with 46 chromosomes in the blood cultures, but a larger proportion of these in the skin cells. Thus, also in this XO/XX group the mosaicism varied between different tissues from the same individual.

Ring chromosome of X

A ring chromosome (X_R) was found in many cells from several tissues from Case 55. These findings have briefly been described earlier in a preliminary report (*Lindsten & Tillinger* 1962).

Essentially, three types of cells were found in this patient: cells with 45 chromosomes and an XO sex chromosome constitution; cells with 46 chromosomes, one ring chromosome and one apparently normal X chromosome (Fig. 6); and cells with 47 chromosomes, two ring chromosomes and one apparently normal X chromosome. The ring chromosome was observed

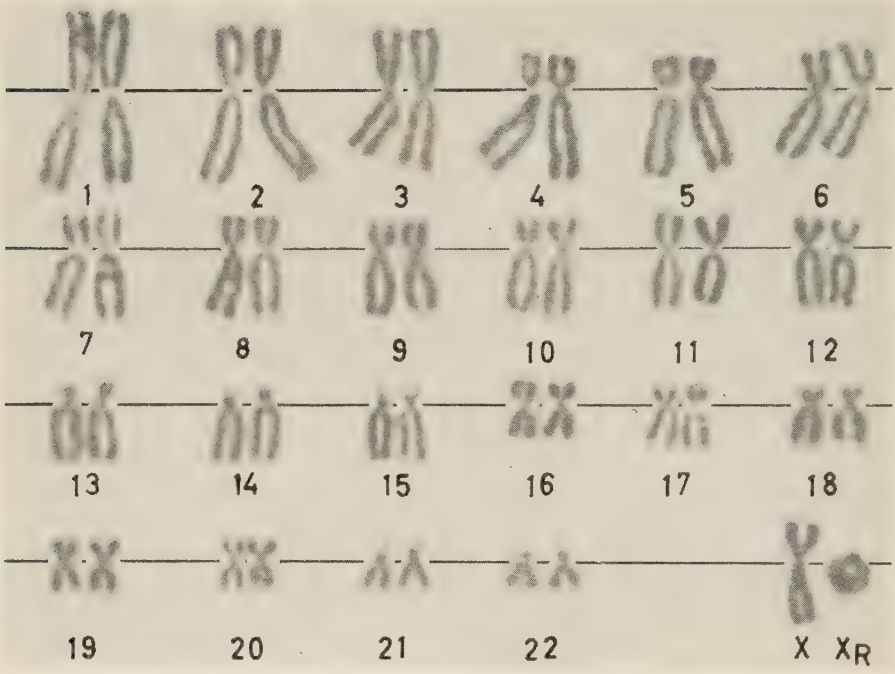


Fig. 6. Karyotype from a mitotic leucocyte from Case 55. 46 chromosomes with one apparently normal X chromosome and one ring chromosome of X (X_R). Acetic orcein stain. Phase contrast. × 2600.

in cells from cultures of peripheral blood and in one biopsy from bone marrow, from skin and from a lymph node, but not in cells from a second skin biopsy or from an ovarian biopsy. The proportion of the different cell types was fairly constant in cultures of seven blood specimens taken on different occasions during one year.

Cells with a ring chromosome were much more uncommon in other tissues than blood, and they disappeared after a few transplantations *in vitro* (see Table 13). The number of sex chromatin positive cells was very low in the primary cultures and decreased simultaneously with the ring chromosome. This elimination of the ring *in vitro* is probably due to the structural rearrangements which are a characteristic behaviour of ring chromosomes (*McClintock* 1938). This finding of ring chromosomes in cells from several tissues, together with the relatively constant proportion of such cells in cultures of peripheral blood speaks in favour of the opinion that cells with a ring chromosome are continuously dividing and not completely eliminated, at least not in lymphoid tissue *in vivo*.

The size of the actual ring chromosome was measured and generally found to be the same as the chromosomes in the group 13–15. There was

also a clear tendency for the ring to be relatively shorter (more contracted) in the early prophases than in the metaphases. Thus, the ring was 96 per cent (standard deviation, S.D., ±11 per cent) of the mean size of the chromosomes in the group 13–15 in 10 early prophases and 128 per cent (S.D. ±9 per cent) in 13 metaphases measured. The difficulties in selecting cells and obtaining accurate measurements of ring chromosomes are obvious, and therefore the validity of these observations cannot be judged at present.

Various types of numerical and structural changes of the ring chromosome were seen in about 10 per cent of the cells with a ring (Figs. 7 and 8 *a*). In *cells with 46 chromosomes*, mono- and dicentric ring chromosomes with increased size were found, the largest ring observed being dicentric and twice the size of chromosome No. 1. No ring chromosomes which could be considered definitely diminished in size were observed. In *cells with 47 chromosomes* the two ring chromosomes were enlarged or of the size generally observed; they were either monocentric or dicentric. In other cells with 47 chromosomes two rings of unequal size were sometimes seen, one enlarged and the other diminished in size (Fig. 8 *a*).

Polyploid cells were also observed, and they contained similar aberrations of the ring chromosomes to the diploid cells. They sometimes contained only one ring.

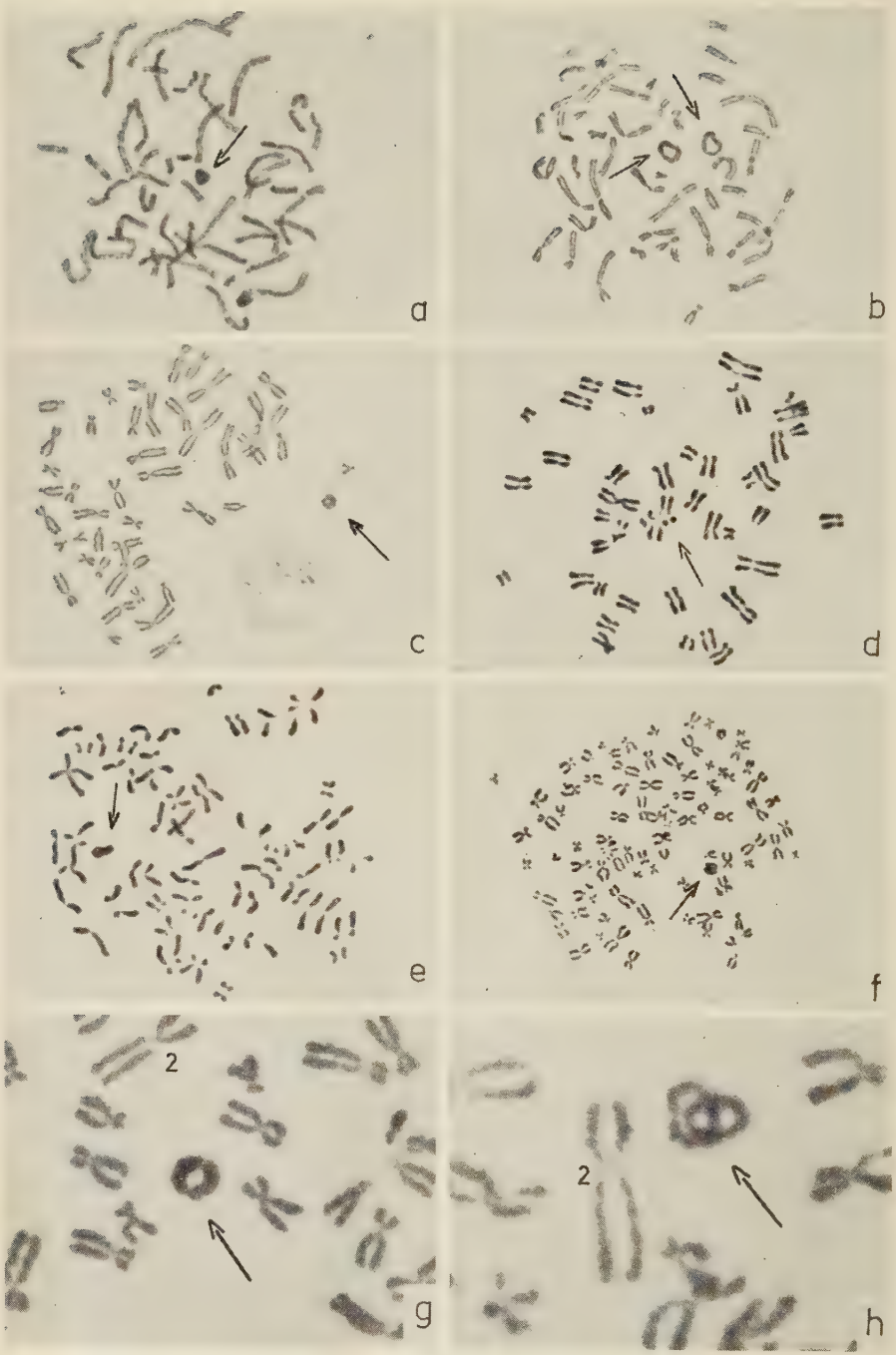
Chromosome aberrations other than ring formations were never observed in this patient, except for the abnormality of one of the chromosomes in the group 13–15 discussed below.

Furthermore, three cells in two different tissues were found to have 47 chromosomes with two extra chromosomes in the group 6-12-X. The origin of these cells is unknown.

Micronuclei were observed in 0.6 per cent of 3000 mononuclear cells, almost exclusively monocytes, of blood smears from this patient. These micronuclei probably consisted of acentric chromosome fragments resulting from structural aberrations of the ring chromosome, since they are not found in cells from normal individuals.

The number of aberrations at anaphase and telophase in the long-term cultures were not calculated since the proportion of cells having the ring chromosome was small and the ring was rapidly eliminated.

In addition, another structural abnormality was noted in this patient. One of the chromosomes in the group 13–15, in all cells and tissues analysed, consistently had an abnormally long short arm. Morphologically this looked like a duplication of the short arm with a constriction between the components, and with satellites of normal appearance at the distal ends (Fig. 8 *b*, *c*). The same abnormality was found in the father of the proposita who had an otherwise apparently normal male karyotype. He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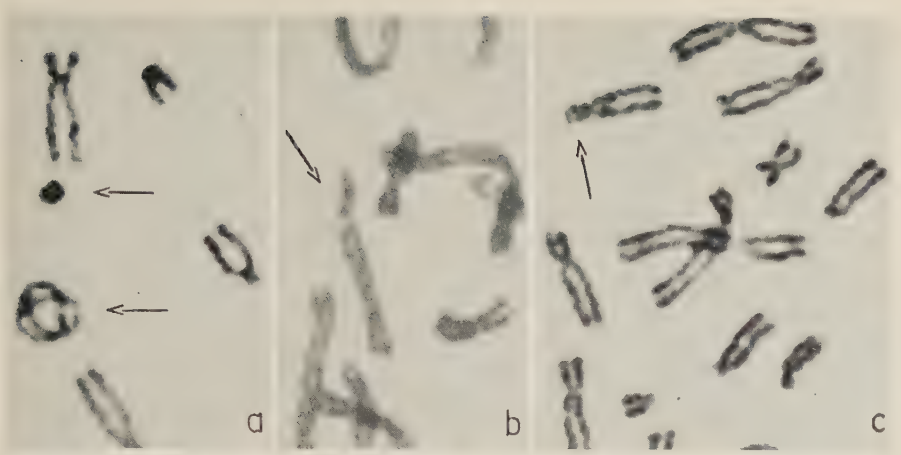

Fig. 8. (*a*) Detail of a mitotic bone marrow cell from Case 55. The arrows are pointing at one enlarged, monocentric ring chromosome and one apparent ring chromosome, which is diminished in size. Acetic orcein stain. Phase contrast. × 2900.
(*b*) Detail of a mitotic leucocyte from Case 55. The arrow is pointing at the abnormal chromosome of the group 13–15. Acetic orcein stain. Phase contrast. × 2500.
(*c*) Detail of a mitotic bone marrow cell from Case 55. The arrow is pointing at the abnormal chromosome of the group 13–15. Acetic orcein stain. Phase contrast. × 2700.

had always been healthy except for arthrosis of the hip joints. The significance of this chromosome aberration cannot be evaluated at present, since it is impossible to decide whether it is only coincidental with, or related to the occurrence of the ring chromosome. A testicular biopsy for meiotic studies could not be obtained from the father. The mother was dead.

Other chromosome constitutions

This group consists of three patients (Nos. 54, 56 and 57).

Case No. 54 had an apparently normal female karyotype in cells from

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Fig. 7. Ring chromosomes from Case 55. All pictures are from cells of cultures of peripheral blood. Acetic orcein stain and phase contrast were always used.
(*a*) *Prophase:* the arrow is pointing at the ring chromosome, which is of the size generally found in this patient. × 800.
(*b*) *Late prophase:* the arrows are pointing at two enlarged, dicentric ring chromosomes. × 900.
(*c*) *Metaphase:* the arrow is pointing at the ring chromosome, which is of the size generally found in this patient. × 900.
(*d*) *Early anaphase:* the arrow is pointing at the ring chromatids, which seem to be smaller than generally found in this patient. × 900.
(*e*) *Anaphase:* the arrow is pointing at the ring chromatids, which might be interlocked. × 1100.
(*f*) *Teiraploid metaphase:* the arrow is pointing at the large ring complex. × 700.
(*g*) *Detail of a metaphase:* the arrow is pointing at an enlarged, dicentric ring chromosome. Chromosome No. 2 is indicated. × 2400.
(*h*) *Detail of a metaphase:* the arrow is pointing at an enlarged, monocentric ring chromosome. Chromosome No. 2 is indicated. × 3000.

Fig. 9. Karyotype from a mitotic leucocyte from Case 56. 46 chromosomes with one apparently normal X chromosome and one X chromosome with a probable deletion of the short arm (X_D). Acetic orcein stain. Phase contrast. × 2300.

two different tissues. She was also sex chromatin positive in cells from buccal mucosa smears, and had drumsticks in a proportion of the neutrophil leucocytes.

Since the X chromosome cannot be morphologically identified it could not be excluded that this patient might have had a small structural abnormality of the X chromosome. Furthermore, mosaicism could not be excluded although it could not be proved in the two tissues analysed.

Case 56 had a mosaicism in both tissues analysed. A large proportion of the cells were of XO type, and the other cell type had 46 chromosomes with one chromosome missing in the group 6-12-X and one extra chromosome in the group 13–15. The latter chromosome was of the same size as, but clearly different from the chromosomes of the group 13–15 since it lacked the short arm. It was interpreted as a deletion of the short arm of X (X_D) (Fig. 9). The patient had drumsticks in a proportion of the neutrophil leucocytes and was sex chromatin positive in cells from buccal mucosa smears. The sex chromatin bodies were considered somewhat smaller than normal, and objective measurements of their area and DNA content will be discussed on pp. 35.

Case 57 was found to have only cells with an XO sex chromosome constitution in two different tissues. Since she was sex chromatin positive in cells from buccal mucosa smears but negative in sections from a skin biopsy which was also cultured and found to have an XO constitution and to be sex chromatin negative, mosaicism was strongly suspected but could not be proved.

The interpretation of the cytogenetical findings in the present material reveals the following:

1. Of 57 patients with Turner's syndrome 35 were found to have an XO sex chromosome constitution, 11 a presumptive iso-chromosome for the long arm of X (X_I) nine of which had mosaicism. Seven cases had an XO/XX mosaicism, one an apparently normal female karyotype, one a ring chromosome of X (X_R) with mosaicism, one a deletion of the short arm of X (X_D) with mosaicism, and one a mosaicism of unknown type. In no case was a Y chromosome found.

2. Altogether 19 out of 57 patients had mosaicism. The mosaicism was most common in the patients with structural abnormalities of the X chromosome.

3. The mosaicism varied between patients and between different tissues as well as within one tissue from the same individual.

4. In no case was there any evident discrepancy between sex chromatin and chromosome findings, i.e. cells with more than one X chromosome probably had a sex chromatin body.

DNA content of sex chromatin and nuclei

The results of the DNA measurements and their statistical analysis will be discussed in detail elsewhere (*Klinger, Lindsten, Fraccaro & Barrai,* in preparation).

The DNA content of sex chromatin and nuclei was measured in cells from Turner patients with structural abnormalities of the X chromosome, from control individuals with two apparently normal X chromosomes, from one patient with an XXXY, one with an XY/XXY and two with an XXXXY sex chromosome constitution. Cells of buccal mucosa smears and cells obtained from skin biopsies and grown *in vitro*, were used. The latter cells had generally been transplanted once or twice and grown for two to three weeks *in vitro*. For most subjects preparations were made more than once, and all preparations from different patients and controls processed simultaneously were defined as one series. All series were prepared in a uniform way.

Two types of measurements were made for each nucleus; the DNA index

of the nucleus (N/DNA), and of the DNA value of the sex chromatin (S/DNA). Means and variances of N/DNA and S/DNA were calculated separately for each series. The consistency between series from the same individual was tested by analysis of variance. This revealed considerable variability, and the means were occasionally significantly different. Since it is difficult to conceive that there should be systematic variations of DNA content with time, the observed inconsistencies are likely to be due to technical variations despite the attempt to standardise the procedure.

The regression of S/DNA on N/DNA was almost invariably significant and consistent within patients, i.e. there were no significant differences between various series within the same patient. In other words, in each patient S/DNA and N/DNA were significantly correlated. It should be noted that not all patients were included in every series, which made impossible a single analysis of variance "between series and patients". However, in those instances in which a patient was represented in at least two series the regressions were not significantly heterogeneous.

Before a comparison can be made between different individuals, the variations due to technical factors have to be eliminated. Considering that N/DNA should be constant in all cells with the same karyotype and taking advantage of the significant regression of S/DNA on N/DNA, variation due to technical inconsistencies could efficiently be eliminated by equalising N/DNA for all individuals. Equalisation was carried out through analysis of covariance, and the means of S/DNA were corrected accordingly. Heterogeneity of S/DNA "between series within patients" was not significant when tested after correction. This permitted pooling of data from different series. Thus, a *single corrected mean* was obtained for each individual and the differences between means may be tested for significance. Uncorrected and corrected means of S/DNA together with means of N/DNA and number of cells analysed are shown in Tables 2 and 3. Inspection of the tables reveals the significance of the correction.

Analysis of the buccal mucosa smears showed that Cases 44 (XX_I) and 38 (XO/XX_I) had significantly higher S/DNA than Cases 40 (XO/XX_I) and 56 (XO/XX_D), than the Controls D, A and B and than XXXXY (S) but not than the others. Case 40 (XO/XX_I) was not significantly different from Case 41 (XO/XX_I). There was a considerable overlapping of the standard deviations of the corrected means for S/DNA of buccal mucosa smears.

Furthermore, the analyses of cells grown *in vitro* revealed that, of the cases with a presumptive iso-chromosome, Nos. 44 and 41 had significantly higher S/DNA than all the others, and that Case 38 (XO/XX_I) had significantly higher S/DNA than all the other cases except XY/XXY and Control I.

TABLE 2. *DNA content of sex chromatin and nuclei in cells from buccal mucosa smears.*

Subject	No. of nuclei	Means N/DNA	Means S/DNA	"Corrected" S/DNA means
XX_I (Case 44)	55	50.44	8.43	8.41±.45
XO/XX_I (Case 38)	49	55.39	8.40	8.06±.48
XX_I (Case 36)	52	41.41	7.08	7.63±.47
XXXY	55	49.51	7.57	7.61±.45
XO/XX_I (Case 41)	26	34.58	6.58	7.57±.66
XXXXY (W)	53	66.54	8.50	7.45±.48
XX (Control C)	26	56.72	7.77	7.35±.65
XO/XX_I (Case 40)	90	46.83	7.29	7.08±.35
XX (Control D)	24	46.80	6.81	7.02±.68
XXXXY (S)	166	49.53	6.60	6.63±.26
XX (Control A)	54	63.47	7.41	6.55±.47
XX (Control B)	31	27.39	4.87	6.32±.63
XO/XX_D (Case 56)	25	49.95	5.34	5.35±.66

In conclusion the results indicate, especially in the *in vitro* set, that sex chromatin in cells with a presumptive iso-chromosome for the long arm of X contains more DNA than controls with two apparently normal X chromosomes. The single sex chromatin bodies of XXXY and XXXXY cases did not have more DNA than the controls in the present material. The cells with a probably deleted X chromosome had consistently the lowest values observed in both sets of results.

TABLE 3. *DNA content of sex chromatin and nuclei in cells grown in vitro.*

Subject	No. of nuclei	Means N/DNA	Means S/DNA	"Corrected" S/DNA means
XX_I (Case 44)	25	42.00	8.52	9.76±.64
XO/XX_I (Case 41)	31	46.86	8.79	9.64±.60
XO/XX_I (Case 38)	25	34.16	6.84	8.73±.66
XX (Control I)	25	73.32	8.92	7.59±.64
XY/XXY	25	98.91	10.68	7.25±.74
XX (Control II)	24	43.18	5.92	7.07±.65
XX (Control III)	25	74.94	8.40	6.94±.64
XXXXY (S)	112	63.73	7.43	6.89±.70
XX (Control IV)	25	70.29	7.92	6.84±.63
XX Mosaic Mongol	22	64.00	6.86	6.30±.66
XXXY	39	41.09	4.90	6.22±.52
XO/XX_D (Case 56)	40	35.24	4.21	6.01±.53

The areas of sex chromatin and nuclei were measured in cells of buccal mucosa smears from normal adult females with two apparently normal X chromosomes, and from some of the patients in the present material who had structural abnormalities of the X chromosome. The results are given in Table 4.

There was no correlation between the area of the sex chromatin and that of the nuclei. As seen from the table, the mean sex chromatin areas from the cases with presumptive iso-chromosomes were larger than those from the two normal controls and from the case with the probably deleted X. The latter had the smallest area of the whole group studied. The area of the sex chromatin in the case with an XXXXY constitution was not different from that of the controls, and the standard deviation showed overlapping with one of the cases with a presumptive iso-chromosome (No. 44). There was also a considerable overlapping of the standard deviations of other individual cases. The average of the mean areas of the three iso-chromosome cases (0.90, S.D. ± 0.028 cm^2) was significantly larger than that of the corresponding average for the normal controls (0.63, S.D. ± 0.018 cm^2) ($0.001 < p < 0.01$). The difference in mean area was not significant between the pooled normal controls and the case with a probable deletion of the short arm of X.

These findings support the results obtained by analysis of the DNA content of sex chromatin and nuclei (see pp. 35). They show that even with objective measurements the differences in the area of the sex chromatin between apparently normal and the present types of structurally abnormal X chromosomes are not always consistent. However, there is a clear tendency to a larger area of the sex chromatin in the presumptive iso-chromosome cases and to a smaller area in the case with the probably deleted X.

Table 4. *Area of the sex chromatin in cells from buccal mucosa smears.*

Patient	No. of nuclei	Mean area, cm^2	95 per cent confidence limits
XX_I (Case 36)	123	1.016 ± 0.062	$1.138 - 0.894$
XO/XX_I (Case 38)	87	0.926 ± 0.032	$0.989 - 0.863$
XXXXY (S)	87	0.759 ± 0.025	$0.809 - 0.709$
XX_I (Case 44)	101	0.726 ± 0.026	$0.777 - 0.675$
XX (Control 1)	60	0.682 ± 0.033	$0.748 - 0.616$
XX (Control 2)	97	0.589 ± 0.019	$0.627 - 0.551$
XO/XX_D (Case 56)	83	0.483 ± 0.022	$0.527 - 0.439$

DNA synthesis of structurally abnormal X chromosomes as revealed by ^{3}H-thymidine labelling

Cultures of leucocytes from patients with probable structurally abnormal X chromosomes were labelled with ^{3}H-thymidine in order to study the detailed pattern of chromosome duplication, i.e. whether the individual chromosome duplication is of random nature or follows a definite time-sequence. Labelling experiments were performed in cases with the following presumptive sex chromosome constitutions: XX_I (No. 44); XO/XX_I (No. 46); $XO/XX_RX_RX_R$ (No. 55).

Entire chromosomes, as well as discrete segments of the chromosomes, incorporate sufficient ^{3}H-thymidine to render them visible by the autoradiographic technique used. Cells, which have reached prophase or metaphase two and a half to three hours after the injection of ^{3}H-thymidine into the medium, demonstrated labelled chromosomes. The labelling was not uniform, since the rates of synthesis of DNA units at different sites vary at the time of exposure to the isotope. The dividing cells in this system have a two to three hour period between the end of the DNA synthesis and the onset of mitosis. Hence, with the incubation time used, i.e. three to four hours, the cells appearing in mitosis at the end of this time must have been near to, or have just passed the end of the synthesising period. This is indicated by a high proportion of unlabelled metaphases (30–50 per cent). The total duration of the synthesising period is not accurately known, but grain counts of the labelled mitoses compared with those of the labelled interphase nuclei indicated that, on the average, the labelled mitosis contained only about one-fifth of the total number of grains. The labelled metaphases studied therefore probably took no more than 30 minutes of the synthesising period, and with the labelling system used in these studies this would have been at the very end of that period. The metaphases selected for analysis were relatively free of overlapping chromosomes, and were lightly labelled in order not to obscure the morphology of the underlying chromosome.

In a proportion of cells in metaphase from *normal females* one heavily labelled chromosome was observed (Fig. 10 *a*) (e.g. *Gilbert et al.* 1962). This distinctly labelled chromosome met the morphological criteria of the supposed X chromosome, and accounted for 14.4 per cent of all the grains in the 33 cells analysed in great detail. In many cells this was the only chromosome with detectable labelling. The tentative identification of this chromosome as one of the X chromosomes has been confirmed by other workers (*German* 1962, *Morishima et al.* 1962). Furthermore, it seemed that in lightly labelled cells, the apparently normal X chromosome had a heavier labelling pattern near the centromere in the long arm.

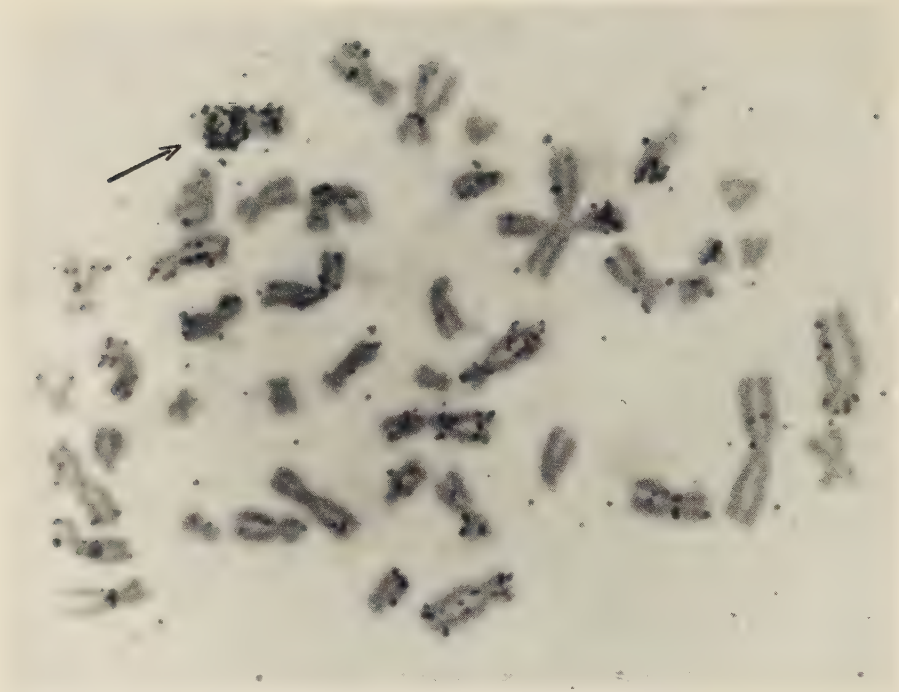
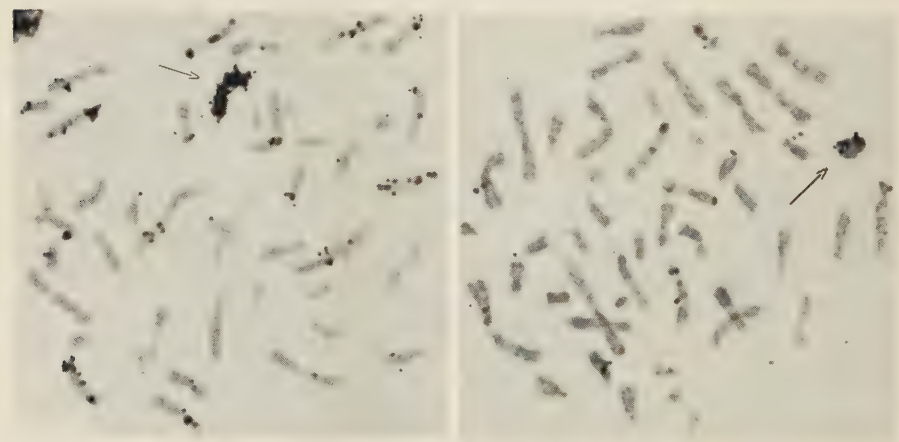


Fig. 10. Labelling with ^{3}H-thymidine of mitotic metaphases in leucocytes from cultures of peripheral blood. 46 chromosomes. Leishman-Giemsa stain, ordinary light. Fig. 10 *a* and *b* were provided by Dr. *S. Muldal,* Manchester, and Fig. 10 *c* by Dr. *Janet Rowley,* Chicago.

(*a*) Cell from a normal female. The arrow is pointing at the heavily labelled chromosome presumed to be of the X chromosome. × 1700.



(*b*) (*c*)

(*b*) Cell from Case 44. The arrow is pointing at the heavily labelled chromosome presumed to be the iso-chromosome. × 1700.

(*c*) Cell from Case 55. The arrow is pointing to the heavily labelled ring chromosome. × 1300.

According to the particular labelling system used, the proportion of cells showing intense labelling of one X chromosome in the female will vary, as will the per cent grain carried by the "hot" X in a cell. The total number of grains over a cell probably indicated how near that cell was to the end of the synthesising period when the isotope was applied. As the end of this period is approached, the relative difference between the number of grains on the "hot" X and on the other chromosomes, becomes more marked, which indicates that synthesis of the *whole* "hot" X chromosome occurs at the very end of the period (*Gilbert et al.* 1962, *Rowley et al.* 1963). Furthermore, the rate of synthesis of this chromosome was faster than for other chromosomes of similar size. It is difficult to decide whether all cells contained "hot" X chromosomes because of the high proportion of unlabelled mitoses due to lack of synchrony between cells, and due to the correlation between the proportion of grains of the "hot" X chromosome and the total number of grains.

Cells from *normal males,* prepared in the same way, do not contain this "hot" chromosome, although the labelling pattern with regard to the other chromosomes, except for the Y chromosome, is similar to that of normal females (*Morishima et al.* 1962, *Muldal et al.,* in preparation).

In the present work the "hot" chromosome was absent in cells with a supposed *XO constitution* from two cases with mosaicism (Nos. 46 and 55). No differences were otherwise observed between these cells and those from normal females.

The presumptive *iso-chromosomes for the long arm of X* appeared to be heavily labelled at the end of the synthesising period, and to be the only heavily labelled chromosome in cells with this structural abnormality (Fig. 10 *b*). The possibility that the supposed normal X chromosome might have been hidden under particularly large grain groups was checked through careful analysis of the number and morphology of the other chromosomes. Visual examination of the grain distribution of heavily labelled chromosomes showed a remarkable degree of symmetry of the two arms. This was most easily observed in lightly labelled cells. The arms of the presumptive iso-chromosomes were subdivided into three parts, and the variance of the differences in grain counts of corresponding parts of the two arms were calculated and compared with the variance of the sums of these counts. This analysis was compatible with the concept that the two arms might be homologous and symmetrical around the centromere.

The "hot iso-chromosome" accounted for 16.9 per cent of all grains in the cell. The regression curve of the proportion of grains over this chromosome as compared with the total number of grains over the cell, was found to lie parallel to and above the curve for pooled XX cells and cells with a supposed XXXXY constitution. The curves could be made to overlap by

reducing the scores for the iso-chromosome by a factor of one-sixth. This represents the approximate difference in length between a supposedly normal X chromosome and a presumptive iso-chromosome.

The detailed grain analysis discussed above, was made in 25 cells from Case 44 and has been published recently by the author (*Muldal et al.* 1963). In the same case another 25 cells were used, but only for the study of the presumptive iso-chromosome *per se*. In addition, similar labelling patterns were observed in Case 46.

Labelling of cells with one apparently normal X chromosome and one *ring chromosome* (Case 55), consistently revealed that only the latter chromosome was "hot" (Fig. 10 *c*). An analysis of grains in 60 cells indicated that, on the average, the ring chromosome amounts to about 60 per cent of a supposedly normal X chromosome. As is apparently the case in the supposedly normal X chromosome, the ring appeared to be asymmetrically labelled around the centromere. This suggests that the actual ring chromosome arose from the union of the ends, formed by a break in each arm, and hence that it contained material from both arms of X.

Studies on colour-blindness and the blood group Xg

Colour-blindness and the blood group Xg are sex-linked inherited. They may therefore serve as marker genes in the study of numerical and structural aberrations of the X chromosome.

The results of the studies with these markers have been reported earlier (*Lindsten et al.* 1963 *a, b, c*).

Colour-blindness

The detailed results are given in Table 13.

Five patients out of 54 (Nos. 18, 30, 38, 52 and 57) were found to have colour-blindness, all of the deutan type. Two out of 32 with an XO constitution were colour-blind. These two frequencies, 9.3 and 6.1 per cent, agree with those reported previously by *Polani et al.* (1956) and *de la Chapelle* (1962). Only in the latter material were the chromosome constitutions of the patients analysed.

Of the five colour-blind patients in the present material, Nos. 18 and 30 had an XO sex chromosome constitution. In No. 18 the mother was probably a carrier, while in No. 30 the father was colour-blind (see Case reports). These two XO patients therefore must have received the X chromosome from the mother (No. 18) and father (No. 30), respectively.

Case 38 had an XO/XX_I mosaicism and will be discussed below in connection with the blood group Xg.

Case 52 was an XO/XX mosaic. The father was unknown, therefore it was not possible to find out from which of the parents she had received the gene for colour-blindness.

Case 57 and her father were colour-blind. Only XO cells could be found in biopsies from two different tissues of the patient. However, mosaicism was strongly suspected, since she was sex chromatin positive in cells from buccal mucosa smears. Thus, the case demonstrates the difficulties in drawing conclusions from the simultaneous occurrence of abnormalities of the X chromosome and sex-linked genes.

The Xg blood group

The detailed results are given in Table 19.

Blood from 22 patients with an *XO sex chromosome constitution* and their parents could be analysed for the Xg blood group. As seen from Table 19 one of these patients (No. 9) had the paternal X chromosome since both the patient and her father were Xg(a^+) and her mother was Xg(a^-). Furthermore, nine patients (Nos. 1, 6, 11, 13, 15, 17, 18, 23 and 29) had the maternal X chromosome since either were the patients and their mothers Xg(a^+) and their fathers Xg(a^-), or the patient (No. 6) Xg(a^-) and her parents Xg(a^+). In one of the above cases (No. 18) this result is in agreement with the one obtained on the basis of colour-blindness. The patient was colour-blind and the mother a carrier (see above), which confirmed that the patient had received the mother's X chromosome. As seen from the pedigree (see Case reports), the mother of this patient must have had one X chromosome carrying the gene Xg(a^+), and the other one carrying the gene for colour-blindness. From this it follows that three out of five individuals of the sibship (the proposita and her two brothers) had genotypes which probably were the results of crossing over.

Xg was also studied in eight families, to which patients with an *iso-chromosome for the long arm of X* belonged. In one of these patients (No. 38) information concerning the localisation of the genes for deutan colour-blindness and Xg could be obtained (see pedigree in the Case reports). If the iso-chromosome hypothesis discussed on pp. 67 is true, and since both parents were Xg(a^+) and the proposita Xg(a^-), the iso-chromosome in this patient must have originated from the father's X chromosome. Furthermore, the mother must have been heterozygous for Xg, and the gene Xg ought to be located on the short arm of X. The same reasoning with regard to gene localisation should similarily apply to deutan colour-blindness in this case. However, there was some difference between the results obtained by the Ishihara charts and those with the anomaloscope. In addition, the phenotype of an individual having two genes for

colour-blindness and one for normal colour vision is unknown. Cases 36 and 40, where the patients also were Xg(a$^-$) but the mothers Xg(a$^+$) and the fathers Xg(a$^-$), would also add evidence to this hypothesis provided it could be shown that the mothers were homozygous. If the gene Xg is located on the short arm of X, the iso-chromosomes of Cases 37, 41 and 44 would also be of paternal origin. These results will be treated further in the Discussion in the light of findings regarding the behaviour of normal and structurally abnormal X chromosomes presented on pp. 71.

As mentioned above, patient No. 38 was colour-blind. If the mother had the gene Xg on one X chromosome and the gene for colour-blindness on the other, two individuals out of five in this sibship would have genotypes resulting from crossing over. On the other hand, if the mother had both genes on the same chromosome, three of the genotypes found would be the results of crossing over. Combining the data concerning crossing over from Cases 18 and 38 it can be seen that five or six out of 10 individuals had genotypes resulting from crossing over between the genes for Xg and deutan colour-blindness. This frequency fits with the one reported by *Jackson et al.* (1962) for the same genes.

In only one family (Case 50), where the patient had an *XO/XX mosaicism,* could blood be obtained. The proposita and her father were Xg(a$^-$) and the mother Xg(a$^+$). Because of this finding no information regarding non-disjunction could be obtained.

In none of the cases studied did the results of the other blood groups or serum protein groups exclude maternity or paternity.

The data obtained by analyses of deutan colour-blindness and the blood group Xg may be summarised as follows:

1. Out of 11 cases with an XO constitution nine had received the maternal and two the paternal X chromosome.

2. Crossing over between the genes for deutan colour-blindness and Xg occurred in five or six out of 10 individuals.

3. The genes for deutan colour-blindness and Xg may be located on the short arm of the X chromosome.

Pedigree analysis

The detailed results are given in Table 14. All control data were obtained from *Official Statistics of Sweden* (1901–1960).

Maternal age at the birth of the patients

The distribution of the maternal age at the birth of the propositi in the present material and in a control material from the general Swedish

TABLE 5. *Maternal age at the birth of the patients.*

The material has been divided into groups according to the sex chromosome constitution of the propositi.

Maternal age, years	No. of cases			Control distribution	
	XO	Other constitutions	All cases	Per cent	Expected, *n*
⩽20	2	—	2	2.77	1.58
20–24	7	6	13	21.65	12.34
25–29	9	6	15	30.31	17.28
30–34	10	5	15	24.46	13.94
35–39	7	4	11	14.97	8.53
⩾40	—	1	1	5.84	3.33
Total	35	22	57	100.00	57.00
Mean age	29.6	29.7	29.6	—	29.8
Variance	36.4	32.3	33.6	—	36.0

population is shown in Table 5. No differences were observed between groups when the material was divided according to the sex chromosome constitution of the propositi. Since most of the propositi were born between 1931 and 1950, the control material was collected from these years and consisted of about 1.9 million married Swedish mothers.

The mean age of the control material, 29.8 years, did not differ significantly from that of the mothers of the Turner patients, 29.6 years, nor did the variances for the two materials show any difference. Thus, the pattern of the two age distributions was found to be the same.

TABLE 6. *Observed and expected distributions of the patients over age of the mother at childbirth in families with two or more children.*

The material has been divided into groups according to the sex chromosome constitution of the propositi.

Maternal age, years	XO		Other constitutions		All cases	
	Observed, *n*	Expected, *n*	Observed, *n*	Expected, *n*	Observed, *n*	Expected, *n*
⩽20	2	1.08	—	1.15	2	2.23
20–24	6	6.23	5	3.32	11	9.55
25–29	9	9.28	5	5.97	14	15.25
30–34	7	7.82	5	5.53	12	13.35
35–39	6	4.80	4	2.37	10	7.17
⩾40	—	0.78	1	1.67	1	2.45
Total	30	29.99	20	20.01	50	50.00
Mean age	29.2	29.4	30.0	29.8	29.5	29.5
Variance	—	—	—	—	33.5	33.1

The method of internal control estimates was also applied, and the results are given in Table 6. Since only families with at least two children were taken into consideration, the total number of cases became 50. The estimation of expected numbers of mothers was made for one-year age groups, and later summarised to five-year age groups. There were 30 mothers and 95 records of age at childbirth in the XO group and 20 mothers and 67 records in the group Other constitutions. Six half-brothers and one half-sister of the propositi on the mothers' side were included. Information could not be obtained for one brother of Case 53. There was good agreement between observed and expected distributions both in the different groups, XO and Other constitutions, and in the whole material.

The present results differ somewhat from those of *Penrose* (1961) who reported a bimodal tendency in the distribution of maternal age in Turner's syndrome. However, as in the material of *Penrose*, the mean maternal age was "not much increased above the average for the general population". Furthermore, *Lenz* (1959) found no evidence of maternal age influence in "chromatin-negativen *Ullrich–Turner*-Syndrom", and *Boyer et al.* (1961) did not obtain any significant difference between observed and expected means for parental age in "chromatin-negative patients with Turner's syndrome". *Polani* (1962) reported a normal maternal age in various groups of patients with this disease and with different sex chromosome constitutions. However, a small "tail" of advanced maternal ages was also observed.

Paternal age at the birth of the patient

Information on paternal age at the birth of the propositi was obtained in 55 cases, and the results are summarised in Table 7. There was neither any significant difference between various groups when the material was divided according to the sex chromosome constitution of the propositi, nor between the whole material and the controls. The mean age was 33.5 years both in the present and in the control material. Furthermore, there were no significant differences between the observed and expected distributions when the method of internal control estimates was used. All married fathers in Sweden during 1931–1950 were used as controls, but the records of paternal age at childbirth in the Official Statistics of Sweden only permits an estimation of the mean age and variance.

Boyer et al. (1961) found no influence of paternal age on the occurrence of Turner's syndrome. There were no apparent differences between paternal age in various groups with different sex chromosome constitutions (*Polani* 1962).

TABLE 7. *Paternal age at the birth of the patients.*

The material has been divided into groups according to the sex chromosome constitution of the propositi.

Paternal age, years	No. of cases			Control distribution
	XO	Other constitutions	All cases	
⩽24	4	—	4	5.2
25–29	6	5	11	14.0
30–34	7	10	17	15.1
35–39	11	2	13	11.0
40–44	5	2	7	6.0
⩾45	1	2	3	3.7
Total	34	21	55	55.0
Mean age	33.3	33.9	33.5	~33.5

BIRTH ORDER

The method of internal control estimates was used for the study of the effect of birth order on the occurrence of Turner's syndrome. The results are given in Table 8. There was good agreement between the observed and expected distributions both in the groups XO and Other constitutions and in the whole material.

Because of residual fertility some errors might be involved when using the above method. A movement upwards of the *expected* distribution could

TABLE 8. *Birth order in families with two or more children.*

The material has been divided into different groups according to the sex chromosome constitution of the propositi.

Birth order	XO		Other constitutions		All cases	
	Observed, *n*	Expected, *n*	Observed, *n*	Expected, *n*	Observed, *n*	Expected, *n*
1	13	11.0	4	6.9	17	17.9
2	12	11.0	8	6.9	20	17.9
3	2	5.0	4	3.4	6	8.4
4	2	2.0	3	1.7	5	3.7
5	—	0.5	1	0.7	1	1.2
6	—	0.1	—	0.3	—	0.4
7	1	0.1	—	0.1	1	0.2
>7	—	0.3	—	—	—	0.3
Total	30	30.0	20	20.0	50	50.0
P-value	0.30–0.50		0.30–0.50		0.70–0.80	

TABLE 9. *Calculation of the "observed" and expected distributions of birth order taking into account residual fertility.*

Birth order	1	2	3	4	5	6	>6	Total
"Observed" distribution	18	20	6	5	1	—	1	51
Expected distribution	17.8	17.8	9.3	3.6	1.6	0.4	0.5	51.0

occur. In the present material there were eight mothers below 45 and five below 40 years of age in the XO group, and four below 45 and one below 40 years of age in the group Other constitutions. If we assume that all mothers below 40 years will have one more child, the distribution given in Table 9 is obtained. This *"observed"* distribution and the expected one are in good agreement and they also agree with the observed and expected distributions for the whole material (the last two columns of Table 8). Thus, residual fertility will probably not change the conclusions reached above that parental age and birth order were similar in the general Swedish population and in this material of patients with Turner's syndrome.

Lenz (1959) reported a high proportion of first-born children among chromatin negative Turner's syndrome. However, *Boyer et al.* (1961) found no significant difference between observed and expected birth ordinals.

SEX RATIO AMONG SIBS

As mentioned earlier all information regarding family data was obtained only by personal interviews with the propositi and/or one of the parents and not through the parish books. Therefore it cannot be totally excluded that the data regarding more distant relatives in the present material are not complete, and thus the data have been interpreted with some caution.

A summary of the observed numbers of males and females among full sibs in different groups of sibships is shown in Table 10. The propositi, mothers, fathers and half-sibs in the respective sibships are excluded. There was a deficiency of females among the sibs of propositi with an XO constitution and with a presumptive iso-chromosome, but the differences when tested by χ^2 analysis, were not statistically significant. A statistically significant deficiency in the number of female sibs ($0.02 < p < 0.05$) was, however, obtained when these two groups were taken together, and also for the whole material. The differences are more accentuated if half-sibs are included. However, studies on larger groups of sibships are required before these results can be considered as consistent. The sex ratios in the other groups of sibships were normal.

Table 10. *Number of full sibs in different sibships.*

The material has been divided into groups according to the sex chromosome constitution of the propositi.

Sibs	XO	Iso-chromosome	Other constitutions	All cases
Sibs of propositi				
Males	36	17	11	64
Females	24	10	9	43
Mothers' sibs				
Males	54	16	18	88
Females	60	16	16	92
Fathers' sibs				
Males	61	25	12	98
Females	66	22	15	103
Maternal first cousins				
Males	101	41	33	175
Females	103	31	23	157
Paternal first cousins				
Males	104	41	25	170
Females	111	35	16	162

It should also be mentioned in this connection that there was not an increased number of abortions and/or still-births in the mothers of the propositi. The only exception was the mother of patient No. 7, who claimed to have had six abortions, but only two could be verified in her hospital charts.

Frequency of twin births

Information regarding twin births could be obtained in all cases except Nos. 4, 8, 16 and 48. Only complete sibships were used for the statistical analysis. In addition, in Table 11 it is pointed out when a grandparent was one of twins. The control material consisted of all registered twin births in Sweden between 1911–1960, i.e. 1.33 per cent. Still-births were included. Most of the individuals of the present material were born during the same period.

As seen from Table 11, the material was divided into the following groups: the proposita's sibship including children of sibs; the mother's sibship and its descendants including half-sibs of the proposita on the mother's side and their children; and the father's sibship and its descendants including half-sibs on the father's side and their children. There were in all

TABLE 11. *Frequency of twin births in different groups of sibships.*
The material has been divided according to the sex chromosome constitution of the propositi.

Sibships and births	XO	Iso-chromosome	Other constitutions	All cases
Patients' sibships and children of sibs				
No. of births	120	46	47	213
No. of twin births	2[a]	2[a]	—	4
Per cent twin births	1.7	4.3	—	1.9
Mothers' sibships and their descendants				
No. of births	369	122	104	595
No. of twin births	7	4	1	12
Per cent twin births	1.9	3.3	1.0	2.0
Fathers' sibships and their descendants				
No. of births	403	142	88	633
No. of twin births	7[b]	3[b]	2	12
Per cent twin births	1.7	2.1	2.3	1.9
All relatives of the propositi				
No. of births	892	310	239	1441
No. of twin births	16	9	3	28
Per cent twin births	1.8	2.9	1.3	1.9
Lower 95 per cent limit of confidence	1.01	1.34	0.26	1.28

1441 births distributed over 32 families where the propositi had an XO sex chromosome constitution, 11 families where the propositi had a presumptive iso-chromosome, and 10 families where the propositi had other sex chromosome constitutions. The frequencies of twin births were similar and about two per cent in all three of the above groups of sibships. However, the variation was somewhat larger between groups where the propositi had different chromosome constitutions. The frequency of twins in the iso-chromosome group, 2.9 per cent, was considered significantly increased, since its lower 95 per cent confidence limit (1.34 per cent) was the same as the frequency of twins in the general population. The same was true when the iso-chromosome group and the XO group were taken together (frequency 2.1 per cent), but not for the XO group alone (1.8 per cent).

The interpretation of these data is complicated by the fact that the frequency of twinning is gradually diminishing in the Swedish population: 1901–1910 it was 1.48, 1931–1940 1.35, and 1951–1960 1.10 per cent.

Table 12. *Number and sex of the twin pairs in groups of families where the propositi had different sex chromosome constitutions.*

Group	Males	Male and female	Females	Total
Iso-chromosome	4	2	3	9
Other constitutions	3	7	8	18
Total	7	9	11	27[a]
Per cent	25.9	33.3	40.8	100.0
Control, per cent	32.7	37.1	30.2	100.0

The selection of control material is therefore of great importance. It should be noted that still-births were included in the frequency, 1.33 per cent, for the general population. Some twin pairs who died at an early age might have escaped registration in the present material.

The distribution in this material of the twin pairs according to sex did not differ from that of the general Swedish population (Table 12).

It seems likely that there may be an increased frequency of twins in the families of patients with Turner's syndrome. However, studies of larger groups of patients are required before such a statement could be considered proved.

Clinical studies

Malformations

General

A great number of various types of malformations in almost every organ system have been described in Turner's syndrome (see reviews by e.g. *Haddad & Wilkins* 1959, *Hauser* 1961, *Polani* 1961). It was considered desirable to register such changes in the present material with as objective methods as possible. Since this proved to be impossible in most instances, subjective judgments had to be used for the evaluation of anomalies of different kinds, e.g. in secondary hair growth, breast development, implantation of hair on the neck, several radiological findings, etc.

Most of the different malformations described by other authors in patients with Turner's syndrome have been observed in the present material. Many such changes have not been put into the tables or case reports, e.g. asymmetry of ears and face, low set of ears, stocky build with broad shoulders (e.g. Fig. 14 *b*), a large distance between the nipples (Fig. 14 *c*), hypoplastic nails (Fig. 19 *c*), etc. The reason was the difficulty in many instances to decide what could be considered as normal variations.

For many of these variables normal measurements are not available or would be difficult to obtain.

Some malformations could be registered at physical or radiological examinations, and the results are presented in Table 17. Of the malformations, two will be discussed separately: the short stature and findings connected with physical growth in Table 18 and on pp. 57, and the sexual infantilism in Table 20 and on p. 56.

In the following the malformations are presented under the headings, External malformations, Radiological findings and Height of the palate arch.

External malformations

Webbing of the neck (Fig. 18 *b, c*) was observed in 17 of the 57 patients. All of these except No. 48 (XO/XX) and 54 (XX) had an XO constitution but none an iso-chromosome. The three infants did not show typical webbing but rather large, loose skin folds at the back of the neck.

Low implantation of hair (Fig. 18 *f*) was found in 34 out of 53 patients. Bilateral *epicanthic folds* (Fig. 18 *d, e*) were seen in 10 out of 55 cases, and a unilateral fold in No. 17, while none of the subjects with an iso-chromosome demonstrated this malformation.

Oedema was observed in nine out of 51 cases at birth (Fig. 13), usually restricted to the hands and feet and to the lower legs. In one (No. 5), the oedema was still present at the age of 16 years (Fig. 19 *a*). In the present material oedema was observed only in the XO individuals. All the infants studied here had oedema since they were referred for this reason. Histological examinations of skin biopsies from the oedematous parts were performed in Cases 3 and 5 (see Case reports). In No. 3 there were pathological changes of the collagen threads, while the lymph vessels had a normal appearance, and no histological signs of oedema were noted. In Case 5 the lymph vessels were dilated, and oedema was noted especially in the subcutis and some minor changes of the collagen threads were found. Two patients (Nos. 11 and 35) had circumscribed *lymphangiomas,* and another two (Nos. 2 and 3) small *haemangiomas.*

Furthermore, *pyloric stenosis* was found in Case 2, *blue sclerae* in Cases 2, 3, 11 and 21, and *transient luxation of the hip joints* in No. 1. Ten patients out of 55 presented an increased number of *pigmented naevi* (Fig. 18 *a*). Several of the patients had *ophthalmological changes* such as myopia or hyperopia, strabismus, nystagmus or ptosis (Fig. 18 *b, c*).

Progressive cerebellar degeneration of hereditary type was present in Case 41 (XO/XX_1). She was the only subject with this abnormality in her family. Similar types of cerebellar degenerations have recently been described in Klinefelter's syndrome (*Indemini & Ammann* 1961).

None of the patients had sex-linked inherited disorders, e.g. muscular dystrophia or haemophilia (for colour-blindness and the blood group Xg, see pp. 42).

As seen in the case reports four out of 43 patients studied (Nos. 20, 29, 42 and 51) had some *persisting deciduous teeth* or were *lacking some permanent teeth*. Hypodontia was known in individuals of several generations in Cases 42 and 51. The frequency of hypodontia in the present material, 9.3 per cent, did not differ significantly from that of healthy Swedish females which is 5.7 per cent according to *Grahnén* (1956). The third molars were not included in these calculations.

An increased frequency of *coarctation of the aorta* has been considered a characteristic feature in patients with Turner's syndrome (*Polani* 1961). The frequency in the general Swedish population is 0.62 per thousand births according to *Carlgren* (1959). Two patients, Nos. 26 (XO) and 29 (XO), in the present material, had coarctation of the aorta (Table 17) with an increased blood pressure in the arms but not in the legs. In this connection it should be mentioned that *hypertension* was found in another three patients (Nos. 24, 31 and 35), and so far, its cause is unknown. The examinations with regard to the hypertension, however, were not completed.

It was impossible to judge from the present material of Turner's syndrome whether external malformations were more common among patients with one type of chromosome constitution than the other. However, some malformations were only found in the XO group, e.g. coarctation of the aorta, and others were very rare or absent in the XO/XX and iso-chromosome groups, e.g. webbing of the neck, epicanthic folds and oedema of hands and feet at birth.

Radiological examinations (Table 17)

Heart and lungs. — Two patients out of 54 (Nos. 26 and 29) had *coarctation of the aorta,* and another two (Nos. 15 and 36) had an *aberrant right subclavian artery (arteria lusoria)*. All patients except No. 35, who showed slight enlargement of the heart and hypertension, demonstrated normal *heart configurations* and *pulmonary findings.*

Kidneys and ureters. — Twenty-six out of 48 patients demonstrated *malformations of kidneys and ureters.* Two of these had conglomerate kidneys, two had malrotated kidneys, nine horse shoe kidneys, seven a double renal pelvis, and six a clearly cleft renal pelvis. All urinary bladders were found to be normal.

Skeleton. — In several instances the *bone structure* was considered abnormal and the condition was termed "slight dysplasia", indicating minor

alterations, mainly to a sparse, coarse bone type, or "dysplasia", indicating more advanced changes (Figs. 21; 22 *c, d, e;* 25 *b*). There was no evidence of decalcification. Sixteen patients out of 54 had a normal skeletal structure, 13 had "slight dysplasia" and 25 had "dysplasia". The dysplastic structure was in mild cases observed in the pelvis and the vertebral column. In severe cases it was present in the greater part of the skeleton and especially in the pelvis, the vertebral column, around the joints and in the hands. In these cases even the cortices of the bones were affected (Fig. 25 *b*). According to the radiologist the changes were different from those usually seen in osteoporosis. Three patients had had *skeletal fractures* (Nos. 20, 34 and 42). Case 42 had had fractures of the vertebral column without a history of trauma; she had two wedge-shaped vertebrae in the thoracic spine. This finding, however, is typical for traumatic fractures. The other two patients had suffered from traumatic fractures of common type. The skeletal structure of the three infants was apparently normal. In only a limited number of patients could the skeletal structure be compared before and after a long period of oestrogen therapy. No obvious alterations were induced by the treatment, although there was a tendency to a decrease of the dysplastic structure in a few of them. On the other hand, many patients demonstrated typical dysplasia in spite of oestrogen therapy for several years.

Some malformations of the vertebrae were found in addition to the abnormal skeletal structure: *underdevelopment of the distal part of sacrum; spina bifida; thoracic kyphosis, scoliosis* and *kyphoscoliosis* and *fused vertebrae. Cervical ribs,* when present, were not registered since they are rather common, and the exact frequency of this malformation in a normal population is unknown. The *pelvis* was infantile, but not male-shaped, in five patients (Nos. 5, 6, 7, 9 and 41). The *sacrum* was in an almost horizontal position in Case 54 who also showed *underdeveloped hip joints.*

The *sella turcica* was apparently small in seven patients, and showed overbridging by bone tissue in another four of the 48 cases studied. None showed obvious enlargement of the sella turcica. Objective measurements of the sellae were not made.

Shortening of the fourth metatarsal (23 out of 53 patients) and *metacarpal* (30 out of 56 patients) *bones* was a common finding, either unilaterally or bilaterally (Figs. 19 *b, d;* 23 *b*; 25 *a*). In addition, the third and/or fifth metatarsal and metacarpal bones were sometimes short. In one patient (No. 15), only the second metacarpal bones were short. The shortness of these bones was probably not caused by premature closure of the epiphyseal zones since the closure here was synchronous to those metatarsal and metacarpal bones which were of normal length. In a few cases the phalanges were also abnormally short (Fig. 25 *b*).

Abnormalities of the knee joint epiphyses (Fig. 24), first described by *Kosowicz* (1959), was a common finding in the present material (37 out of 55 patients). These changes were generally bilateral, although unilateral changes were observed in isolated instances.

The various elbow joint epiphyses were common sites for abnormalities, which were seen in 38 out of 50 patients and were almost always bilateral (Fig. 22). Cubitus valgus was the most common finding, but in many cases it was caused by an extension defect, and therefore could not be considered real cubitus valgus. A combination of both types was also seen occasionally. No attempt was made to measure the degree of cubitus valgus.

Kosowicz (1962) recently reported an *abnormal angular shape of the proximal carpal bones*. This abnormality was found in 10 out of 46 patients when only more advanced cases were taken into consideration. An underdeveloped ulnar part of the distal radial epiphysis and the radial part of the distal ulnar epiphysis might in these cases explain the abnormal angle (Fig. 23 *a*, *c*). No attempt was made to measure this angle because of the difficulties in getting a constant, fixed position of the hand at the examination.

Further skeletal abnormalities were noted in a few cases: S-shaped and/or short radii and ulnae, underdeveloped scapulae and caput humeri and fusion of some carpal bones, etc.

The present material shows that skeletal abnormalities are very common in patients with Turner's syndrome. The dominant features are the dysplastic skeletal structure and the disturbances in the development of a large number of epiphyseal zones. It is noteworthy that, among all patients, only the three infants and Case 49 (XO/XX) did not demonstrate any of these abnormalities. Furthermore, there were no striking differences in this respect between groups of patients with different sex chromosome constitutions.

Two recent reviews of skeletal abnormalities in patients with Turner's syndrome have been presented by *Leszczyński* (1962) and *Astley* (1963).

Height of the palate arch (Table 17)

Odontological studies, the details of which will be published elsewhere (*Filipson, Lindsten, Almqvist & Lindvall*, in preparation), showed that the mean height of the palate arch for 44 patients was 17.0 mm (S.D. $\pm$ 2.0 mm). No differences were observed when the material was divided into groups with different chromosome constitutions. The normal material for comparison consisted of 40 apparently normal healthy Swedish females between 17 and 28 years of age. The height of the palate arch was 17.1 mm (S.D. $\pm$ 1.9 mm) in this group, and *Lundström* (1948) obtained the figure

of 17.3 mm (S.D. $\pm$ 0.23) in 83 healthy Swedish females between 12 and 40 years of age.

There was thus no difference in height of the palate arch between the present patients with Turner's syndrome and apparently normal females of the same age groups. An increased height is, in the literature, considered a common finding in Turner's syndrome. The present study is the first in which exact measurements of the height were performed.

Gynaecological data

The detailed results are given in Table 20.

There were no malformations of the external genitalia in any of the patients. The four youngest, i.e. the three infants and a girl of eight years (Case 4), had apparently normal external genitalia, and no further examinations of the internal genital organs were made. In most of the other patients, before oestrogen therapy, pubic and axillary hair growth was absent or scanty, and the labiae, clitoris and vagina were infantile. Exceptions were six patients (Nos. 25 and 51–55) with apparently normal or only slightly underdeveloped external genitalia, and who also showed normal or slightly decreased development of the breast. Of these latter six patients, only Case 25 had an XO sex chromosome constitution, while the other five had either XO/XX (Nos. 51, 52 and 53), XX (No. 54) or $XO/XX_R/XX_RX_R$ (No. 55). None of the patients showed hypertrophy of the clitoris.

The uterus was considerably underdeveloped in most patients, and generally no ovaries were palpable per rectum. Only in Cases 51, 52, 54 and 55 was the uterus of apparently normal size before oestrogen treatment but ovaries were palpable only in the last two cases. As mentioned above none of these four patients had an XO constitution. Two patients were found to have a bicornuate uterus (Cases 27 and 49).

Five patients had had one to four spontaneous menstruations and five had had menstrual periods, generally irregular and with long intervals, for one to 16 years. Two of these, Nos. 54 and 55, had had regular menstruations for six and seven years, respectively.

Laparotomy was performed on 17 patients, and the findings are described in the individual case reports and in Fig. 20.

With five exceptions, all mothers and sisters of the patients had had menarche at apparently normal time. The exceptions were Cases 6, 9, 22, 44 and 45 where the mothers, and in Case 22 where the sister, had had their first menstruation at about 17 years of age. In Case 44 the mother was also of short stature (149 cm).

Five patients were married (Nos. 25, 27, 30, 34 and 53) but all marriages were involuntarily sterile. None of the couples had difficulties in sexual intercourse.

Physical growth

The detailed results are given in Table 18.

Birth weight

Information regarding birth weight was obtained in 47 patients. Two of these (Nos. 31 and 44) were twins, and therefore not included in the calculations of the mean birth weight. In 10 of the patients such information was not available, generally because the patient was born at home. In 11 of the above 47 patients the calculated date of birth was not registered on the birth charts, but the mothers stated that the patients were born at approximately the expected time; these cases were included in the calculations. The mean birth weight was 2933 g (S.D. $\pm$ 476 g) for 45 patients. No significant differences were observed between groups of patients with different sex chromosome constitutions: these weights were for the XO group 2955 g (S.D. $\pm$ 480 g), for the presumptive iso-chromosome group 2852 g (S.D. $\pm$ 396 g), and for XO/XX mosaics 3063 g (S.D. $\pm$ 624 g).

The mean birth weight of the 36 patients born within $\pm$ 14 days of the calculated date of birth (3064 g, S.D. $\pm$ 401 g), was significantly lower than that of a corresponding control material of girls from the general Swedish population (3460 g, S.D. $\pm$ 444 g, Dr. *L. Engström*, Stockholm, personal communication).

The mean duration of pregnancy was 274 days (S.D. $\pm$ 14.2 days) for 34 patients, and is normally 281 days (S.D $\pm$ 12.7 days) according to *Seitz* & *Amreich* 1952. The difference was statistically significant ($p < 0.02$). The importance of the influence of the decreased duration of pregnancy upon the lowered birth weight will be assessed when further analysis of the control material has been carried out.

Body height

It was possible in the present material, through information from school health cards, to follow the height of many of the patients for several years, generally from the age of seven. The growth curve for each of these patients is presented in Fig. 26. The case material was divided into groups according to the sex chromosome constitution. Because of the possible location on the X chromosome of genes influencing physical growth (*Jacobs et al.* 1961, *Almqvist et al.* 1963) and the different ages at which oestrogen therapy was started it was thought unadvisable to pool the data on growth.

According to the patients' own information, they had always been short, and had already been examined because of short stature during infancy. As seen from Fig. 26, the age at which the patients passed the lower 3σ limits of the normal height variation varies considerably. It is clearly seen that the growth rate of the patients was slower than normal and that, in some patients, the duration of growth was longer than for normal Swedish females. Some cases demonstrated spontaneous variations in growth rate. It cannot be excluded that this only reflects erroneous measurements of height. The final body height in the 29 patients with closed epiphyseal zones was 142.8 cm (S.D. $\pm$ 5.6 cm). Case 22 was excluded since she had a gibbus. When divided according to different sex chromosome constitutions the following mean heights were obtained: for 15 cases with an XO constitution 143.4 cm (S.D. $\pm$ 5.8 cm), for seven with a presumptive iso-chromosome 141.4 cm (S.D. $\pm$ 5.9 cm), for three XO/XX mosaics 146.7 cm (S.D. $\pm$ 7.1 cm) and for four with other constitutions 140.3 cm (S.D. $\pm$ 2.8 cm). These mean heights are not significantly different. Three patients (Nos. 27, 49 and 50) were above the lower 3σ limit of the normal variation of height but can still be considered to be of short stature. If the patients with open or closing epiphyseal zones are considered, three of the four XO/XX mosaics were unusually tall (Cases 47, 49 and 50; height 150, 152 and 154 cm), while those with an XO constitution and those with an iso-chromosome were of the height generally observed in patients with Turner's syndrome. It cannot be excluded that significant differences in height between these genetically different groups might be demonstrated when data from large groups of patients become available.

Body proportions

In people above 10 years of age the span and body height are approximately equal and the lower measurement (the distance from pubis to sole) half of the height. If a difference of $\pm$ 5 cm is taken as the arbitrary normal range, 17 out of 49 Turner patients had spans and 16 lower measurements outside this range. If on the other hand a difference of $\pm$ 10 cm is taken as the arbitrary normal range five out of 49 had spans, and six had lower measurements outside this range. Case 22 was excluded since she had a gibbus.

There are no normal values available for healthy Swedish females regarding body proportions.

Skeletal age

The skeletal age was usually within the normal range of variation ($\pm$ 1 year) or slightly retarded. The only exceptions showing increased skeletal

age were Cases 37 and 54, where Case 37 had received oestrogen treatment since 13 years of age, and Case 54 had probably normal ovarian tissue (p. 56). One patient (No. 39) at 15 years of age had a skeletal age of + 2 years. Three years later the skeletal age was minus 2–3 years. An increasing difference between chronological and skeletal age after the "puberal" age was reported by *van der Werff ten Bosch* (1959) and *Acheson & Zampa* (1961).

The assessment of skeletal age was sometimes complicated by the fact that the epiphyseal zones of the iliac crests remained partly or completely open for long periods of time. The oldest patient who had this maldevelopment was No. 53 who was 35 years old. Sometimes it could not be decided whether this epiphysis was present.

Body weight

Twenty-six of the 57 patients were overweight when compared with the normal material of *Broman et al.* (1942). However, it is questionable whether this latter material can be used for the comparison since it is composed of growing children while Turner patients of the same height have often stopped growing.

Effect of oestrogen treatment

The effect of oestrogen treatment on skeletal age could be evaluated in ten cases (Nos. 15, 17, 18, 20, 22, 26, 33, 37, 40 and 42). The duration of the treatment was two years or more. Only in two cases (Nos. 20 and 37) did the skeletal age increase. It should be pointed out that the earlier X-ray films could be re-examined only in some cases (see Table 18) and the comparison was made on the basis of a written report on these films.

The effect of this therapy on height could not be evaluated objectively but, as seen in Fig. 26, there were no obvious changes in either direction.

Audiometric analyses

The detailed results are given in Table 17.

Out of 41 patients examined, 28 (68 per cent) demonstrated hearing impairment according to the definition given on p. 18. Of these 28 cases, 20 had a pure perceptive type, five a pure conductive type and three a mixed type with both a perceptive and a conductive component in the hearing impairment. In many instances these changes had not been noted by the patients. The most common type of the pure perceptive hearing impairment was the "dip", which was found in 12 cases. A typical ex-

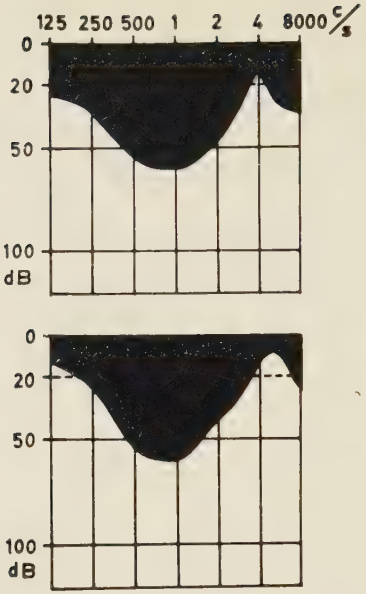


Fig. 11. Tone audiograms from Case 56 at the age of 23 years. Audiogram of the left ear, above, of the right below. For details, see Table 17; c/s, denotes cycles per second, dB, decibels.

ample of such a "dip" in the audiogram is presented in Fig. 11. The parents of three patients with perceptive hearing impairment (Nos. 6, 9 and 17) were found to be within normal limits. The father of Case 56 had a slight perceptive hearing impairment, but her mother was normal. There were no differences between groups of patients with different sex chromosome constitutions.

Previous isolated reports in the literature on the hearing of patients with Turner's syndrome are limited to superficial registrations of the hearing capacity, and the abnormality found has mostly been called "congenital deafness" (e.g. *Schneider* & *McCullagh* 1943). Audiometric analyses have not been reported earlier.

A control material consisting of 5650 boys and 4752 girls has recently been studied (*Wedenberg*, personal communication). This material constitutes 8.2 per cent of all live-born children in Sweden in 1948 and consists of all children in the last class of the elementary school in Stockholm and includes those in schools for children with hearing impairment. All the children were born in 1948 and investigated at about 14 years of age. About 4.7 per cent of the boys and 2.6 per cent of the girls had hearing impairment according to the definition given on p. 18. Almost only perceptive hearing impairment was found: 4.5 per cent of the boys

(1.0 per cent "dips") and 2.4 per cent of the girls (0.9 per cent "dips"). The rest had a conductive or a mixed type of hearing impairment.

Concerning the causes behind the increased incidences of hearing impairment in the present material, one has to take into account the fact that some of the patients had had severe ear infections and some had been operated upon. Another possible explanation could be rubella infection in the mothers, generally during the first trimester of pregnancy (e.g. *Barr & Lundström* 1961). However, although the perceptive hearing impairments among children born to such mothers are to some extent of the same type as those found in the present material, they differ with regard to extension, i.e. the impairment is generally asymmetrical and of the types "total deafness" and "flat loss" in the rubella cases but was usually symmetrical with a "dip" in the patients with Turner's syndrome. Furthermore, according to the birth charts none of the mothers had had obvious signs of rubella during the pregnancies.

Intelligence quotient (IQ)

In the following a summary of the IQ measurements will be given. The results will be discussed in detail elsewhere (*Lindsten, Cronholm & Molander,* in preparation).

The individual IQ values are given in Table 17. The distribution of IQ in all 44 patients studied in this respect and in those with an XO sex chromosome constitution (27 cases) is shown in Fig. 12. The mean IQ value for the total material was 98 (S.D. $\pm$ 15) for the CVB scale, and 94 (S.D. $\pm$ 16) for the SRB scale. Thus, there was a good agreement between the results of the two tests (correlation coefficient 0.87). The means are slightly below the IQ value 100. Because of the differences in selection between this group of patients and the standardisation groups for these scales, the significance of the deviations was not calculated. The mean value for the XO group was 95 (S.D. $\pm$ 16) for the CVB scale, and 91 (S.D. $\pm$ 17) for the SRB scale. As seen from Fig. 12, there was a tendency to a bimodal distribution of IQ in the XO group. When tested with the Sign test (Stanine grades 1–3 versus 7–9) a significant bimodality was found in the XO group, but only for the SRB scale ($p = 0.02$).

There was no tendency to bimodality in the group of patients with other sex chromosome constitutions, but the number of investigated cases was only 17.

These data indicate that many patients with Turner's syndrome have an apparently normal intelligence level but that there is a group of patients, mainly among those with an XO sex chromosome constitution, which demonstrates low values.

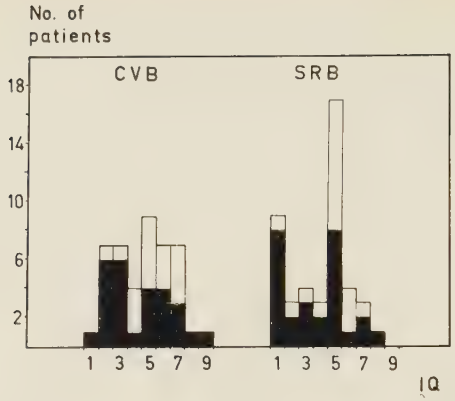


Fig. 12. Distribution of the patients according to IQ. The grades in the stanine scale used here are based on the raw scores of the intelligence tests and have roughly the following IQ equivalents: 1 (< 74), 2 (74–82), 3 (82–89), 4 (89–95), 5 (96–103), 6 (104–111), 7 (112–120), 8 (121–127) and 9 (≥ 128).

The black areas in the figure indicate patients with an XO sex chromosome constitution and the white areas, patients with other constitutions.

The intelligence quotient in patients with Turner's syndrome has earlier been determined in two case materials, by *Hampson et al.* (1955) and *Haddad & Wilkins* (1959). The first authors investigated 16 patients with gonadal agenesis, who were mostly sex chromatin negative, and found a tendency towards a bimodal distribution, one peak being at an IQ of 90–109 and the other at 70–79. The second authors found five patients with an IQ below 80, 12 between 80 and 119, and three above 120 in a material of 20 patients with Turner's syndrome most of whom were sex chromatin negative. In addition eight patients were severely mentally retarded, but no intelligence tests were performed.

Hormone analyses

The detailed results are given in Table 16.

Oestrogen excretion

Most patients had low urinary excretions of biologically and chemically determined oestrogens. Exceptions were Cases 25, 48, 55 and 57, in whom occasionally normal values were obtained. Laparotomy revealed, in Case 55 the presence of ovarian tissue containing follicles, in Nos. 48 and 57 only "streaks". Case 25 was not operated upon. Furthermore, Case 54, on whom an operation was not performed, probably had ovarian tissue since this patient had menstruated regularly for a long time and showed increased excretion of oestrogens during stimulation with chorionic gonadotrophin.

Gonadotrophin excretion

The urinary excretion of total gonadotrophins was increased in most patients. Nine patients had normal (Cases 11, 15, 22, 32, 33, 35, 37, 52 and 55), and three had low values (Cases 26, 36 and 54). Only in the last two patients could the results be confirmed by several estimations. It cannot be excluded that some of the patients with normal gonadotrophin excretion had functioning ovarian tissue. However, it has to be taken into account that the gonadotrophin determinations were routine ones and that the urine collections were sometimes made by the patients at home and such facts may give rise to variations in the values obtained. This can be seen in Table 16, where high and sometimes normal values were obtained in the same patient at repeated determinations.

It is of interest that in three of the four children gonadotrophins could be demonstrated in the urine. Similar findings have been reported earlier by e.g. *Silver* (1951).

During oestrogen therapy the excretion of total gonadotrophins in the urine was lowered and in many cases could not be detected.

Other data

The urinary excretion of 17-ketosteroids and 17 ketogenic steroids was generally normal or in the lower range of the normal variation. However, some individual determinations gave definitely low values.

The serum activity of sulphation factor (SF) was measured in several of the patients, and the results have been published in detail elsewhere (*Almqvist et al.* 1963). Another nine determinations have now been added to the earlier data. Because of the physiological variation of SF with age the material was divided into the age groups 5/12–8/12, 15–20 and 21–42 years of age. Altogether 17 values were increased, 12 were normal and two (Nos. 9 and 37) decreased. The mean value for the first age group was 0.88 (S.D. $\pm$ 0.18), for the second 1.30 (S.D. $\pm$ 0.40) and for the third 1.47 (S.D. $\pm$ 0.47) U/ml. All mean values were significantly increased ($p < 0.001$). No differences were observed between groups of patients with different sex chromosome constitutions.

Other laboratory data

The large number of various laboratory tests performed in the present material is summarised in Table 15. The results obtained fell within normal limits and, with few exceptions, will not be discussed further.

Elliott et al. (1959) reported high levels for acid phosphatase in serum

from patients with Turner's syndrome. This could not be confirmed in the present material.

Lewitus (1962) found increased radio-iodine uptake of the thyroid gland in three patients with Turner's syndrome. The same test in 10 of the present patients gave normal results, and all patients were considered to be euthyroid according to clinical criteria.

The serum level of cholesterol did not differ when the patients had or had not received oestrogen treatment.

There were no incidences of agammaglobulinaemia and no abnormalities were found in the amino acid pattern of urine from five patients.

DISCUSSION

The definition of Turner's syndrome as used in the present study as well as the development of the concept and the genetics of this disease have been discussed in the Introduction. Details regarding the findings obtained have been discussed in the Results. The following discussion will be focused on certain aspects regarding the nature and origin of the various chromosome aberrations observed. Furthermore, a selected number of clinical findings will be discussed in more detail.

In addition to the *XO sex chromosome constitution* originally described by *Ford et al.* (1959) and shortly afterwards by the author (*Fraccaro et al.* 1959) and *Tjio et al.* (1959) two new, structural aberrations of the X chromosome, the *presumptive iso-chromosome for the long arm of X* and the *ring chromosome of X,* have been demonstrated in the present work. Iso-chromosomes had earlier only been found in plants (e.g. *Håkansson* 1933, *Darlington* 1939, 1940) but their presence in man has recently been confirmed by several authors (see *Lindsten et al.* 1963 *b*). Since the original description of a self-perpetuating ring chromosome in man (*Lindsten & Tillinger* 1962) another four patients have been found to have the same type of chromosome aberration (*Turner et al.* 1962, *Wang et al.* 1962, *Smith–White et al.* 1963), but none of these was of the X chromosome, however. Ring chromosomes in man had earlier been reported in tumour cells (*Levan* 1956) and in isolated cells from irradiated patients (*Tough et al.* 1960). The third structural aberration of X found in the present work, the *probable deletion of the short arm of X,* has been reported earlier in one other patient (*Jacobs et al.* 1961). The precise nature of the observed chromosome aberrations and their relation to the X chromosome, will be discussed in the following.

Nature of the chromosome aberrations

The X chromosome in man cannot yet be identified from purely morphological criteria. In spite of this, abnormalities of the X chromosome can be investigated by parallel studies of the drumsticks and of the sex chromatin, the area and DNA content of the latter, and also of the DNA synthesis of the chromosomes. Such studies are based on the fact that drumsticks are found in normal females but not in normal males

(*Davidson & Smith* 1954); that normal males in contrast to normal females do not have sex chromatin (*Barr & Bertram* 1949); and that one of the X chromosomes in cells from normal females synthesises DNA at a later stage of the synthesising period than the other X chromosome and the autosomes (*German* 1962, *Morishima et al.* 1962, *Gilbert et al.* 1962).

The earlier opinion that the two X chromosomes comprise the sex chromatin in cells from normal females has been disproved by later studies showing that, in the rat, the sex chromatin is probably formed by only one of the X chromosomes. The single X chromosome thus constituting the sex chromatin, was considered to be positively heteropyknotic from prophase to metaphase (*Ohno et al.* 1959). *Sandberg et al.* (1960) reported that also in cells from human females one of the X chromosomes was heteropyknotic at metaphase. This latter observation has been confirmed but only for cells in early prophase (*Ohno* 1963). The opinion that only one X chromosome comprises the sex chromatin was also supported by the finding of multiple sex chromatin bodies and extra chromosomes in the group 6-12-X in cells from patients with apparent XXX and XXXXY constitutions, the cells showing mainly two and three sex chromatin bodies respectively (*Jacobs et al.* 1959 *b*, *Fraccaro & Lindsten* 1960 *b*). Furthermore, in cells with the latter two sex chromosome constitutions, two and three entire chromosomes respectively, were found to synthesise DNA simultaneously, late in the synthesising period, as does one of the X chromosomes in cells from normal females (*Morishima et al.* 1962, *Rowley et al.* 1963). A detailed statistical analysis of the grain distribution in the latter work revealed that each of the three "hot" X chromosomes accounted for 11.8 per cent of all grains. This value cannot be directly compared with 14.4 per cent in cells from normal females since these contain only one "hot" X chromosome. If it is assumed that all chromosomes synthesise DNA independently of each other, then the ratio of grains on one "hot" X chromosome to the total number of grains over all the other chromosomes excluding the "hot" X chromosome should be comparable. This ratio was 0.18 for the XXXXY cells and 0.17 for cells from normal females. Furthermore, the regression lines for the proportion of grains labelling the "hot" X chromosomes on the total number of grains for these two cell types showed complete overlap, supporting the conclusion that all the "hot" chromosomes were X chromosomes and were probably those which constitute the sex chromatin.

Therefore, the diagnosis *XO chromosome constitution* in patients with Turner's syndrome was based on the finding of cells with 45 chromosomes and with one of the larger chromosomes in the group 6-12-X missing, on the absence of sex chromatin and drumsticks, and on the absence of heavy labelling of any of the chromosomes with ^{3}H-thymidine late in the syn-

thesising period. The first two criteria were met in the present group of patients with an XO constitution. The third criterion was fulfilled to the extent that there was no heavy labelling with ^{3}H-thymidine in XO cells from cases with mosaicism.

The diagnosis of the *presumptive iso-chromosome for the long arm of X* was based on morphological criteria of the aberrant chromosome, on the apparently increased area and DNA content of the sex chromatin, and on the heavy and symmetrical labelling of this chromosome with ^{3}H-thymidine late in the synthesising period in cells with this chromosome aberration.

The morphological criteria, used to classify the chromosome as an iso-chromosome were its size and the position of its centromere. In addition, the absence of one chromosome in the group 6-12-X, and the presence of mosaicism in combination with XO cells speak in favour of the aberration being an iso-chromosome of X.

Concerning the increased area and DNA content of the sex chromatin in cells with presumptive iso-chromosomes the following may be added. *Jacobs et al.* (1960) reported that the sex chromatin body was apparently smaller than normal in a patient with a probable deletion of the long arm of X. An apparently larger than normal sex chromatin in cells with iso-chromosomes was suggested by *Jacobs et al.* (1961). Objective measurements showed that the area of the drumsticks was significantly increased in leucocytes from patients with an iso-chromosome, and significantly decresaed in those from one patient with a probable deletion involving most of the short arm of X (*Maclean* 1962). In the present work, by objective measurements of the area and DNA content of sex chromatin and nuclei, evidence was obtained that both the area and the DNA content of the sex chromatin was increased in cells from patients with presumptive iso-chromosomes, and apparently decreased in the one case with a probable deletion of the short arm of X.

The significance of the iso-chromosome for the enlargement of the sex chromatin is further supported by the present finding that an abundance of X chromosomes as in XXXY and XXXXY constitutions only gives an increased number of sex chromatin bodies but each with a normal area and DNA content.

Theoretically, if either the apparently normal X chromosome or the iso-chromosome constitute the sex chromatin, one may expect to find a bi-modal distribution of the measurements of its area and DNA content. One would also expect to find that some patients with iso-chromosomes have a normal and some an increased area and DNA content of the sex chromatin. The expected differences are small since the length of the presumptive iso-chromosome is about 3.2 per cent, and the supposedly normal X chromosome 2.5 per cent of the total chromosome length in diploid (XX_1)

cells (*Lindsten et al.* 1963 *b*). No definite bimodality within patients or conclusive differences between patients with iso-chromosomes could be demonstrated. On the other hand, minor differences might have been obscured by the comparatively large overlapping of the distributions of these measurements.

In cells with one apparently normal X chromosome and one with a deletion of the short arm, a bimodal distribution of the area and DNA content of the sex chromatin might similarly be expected. However, no definite bimodality could be demonstrated in this case.

That the structurally abnormal X chromosomes in these cases and not the apparently normal X chromosomes constitute the sex chromatin is also supported by the ^{3}H-thymidine labelling of the chromosomes. When cells with presumptive iso-chromosomes or with ring chromosomes were labelled, these chromosomes, and not the apparently normal X chromosome in the same cells, were found to synthesise DNA late in the synthesising period. Furthermore, the presumptive iso-chromosomes demonstrated an increased total and a symmetrical labelling along their whole length, and had a specific rate of synthesis identical with that of the apparently normal "hot" X chromosome (pp. 39). The symmetrical labelling of the two arms of the presumptive iso-chromosome is of special importance, since differential grain counts over chromosome segments showed that homologous chromosomes did in fact synthesise DNA at the same time (*Gilbert et al.* 1962). Furthermore, late labelling of one part of a sex chromosome did not produce late labelling of its other parts in the Chinese hamster (*Taylor* 1960). In cells from human females the whole X chromosome seems to be heavily labelled, and therefore the numbers of grains over the "hot" chromosomes and the lengths of the chromosomes can be compared in cases with different types of suspected structural abnormalities of X.

Thus, all the above criteria speak in favour of the hypothesis that the aberrant chromosome observed is an iso-chromosome for the long arm of X. There may, however, be other explanations of the nature of a structurally abnormal chromosome of this type such as duplications, translocation between the X chromosome and an autosome, intrachromosomal rearrangement (chromatid interchange) involving breakage and re-union at points close to and on the opposite side of the centromere, and finally crossing over in a pericentric inversion. These mechanisms have recently been discussed in detail elsewhere (*Lindsten et al.* 1963 *b*). It was then pointed out that, in the mouse, an autosomal segment translocated to the X chromosome behaved in its full length as the rest of the X chromosome (*Ohno* & *Cattanach* 1962). On the other hand, the behaviour of the X chromosome in the mouse might be different from that of the X chromosome in man. Furthermore, an apparently identical chromosome

aberration occurring in unrelated but clinically similar individuals supports the hypothesis of a common mechanism of origin which can be repeated in a constant way. This also speaks in favour of the iso-chromosome, as does the observation that no chromosome abnormalities could be demonstrated in the parents and the sibs of three of the patients in the present material.

It should be pointed out, however, that so far there is no evidence from sex-linked genes for the iso-chromosomes hypothesis.

The *ring chromosome* was considered to be an X chromosome for the following reasons: the presence of mosaicism including cells with 45 chromosomes and an XO constitution; the absence of one chromosome in the group 6-12-X in the cells with the ring chromosome; the presence of drumsticks in some of the neutrophil leucocytes, and of sex chromatin in cells from the long-term cultures but not in cells from the buccal mucosa smears; the fact that the ring was labelled with ^{3}H-thymidine late in the period of DNA synthesis; and the fact that grain counts, in agreement with the morphological measurements, revealed that the size of the ring was about 60 per cent of a supposedly normal X chromosome.

Finally, the diagnosis of the probable *deletion of the short arm of* X was based on analoguous evidence to that noted for the ring chromosome and, in addition, on the fact that the area and DNA content of the sex chromatin in cells with this abnormality were decreased.

The above findings have some further implications for the discussion of the nature of the sex chromatin. One of the criteria used for deciding the nature of the aberrations of the X chromosome was the size of the sex chromatin, i.e. its area and DNA content. Thus, the interpretation of the presumptive iso-chromosome for the long arm of X was based on an increased size, and the probable deletion of the short arm of X on a decreased size of the sex chromatin. If these interpretations are correct, then they strengthen the hypothesis that one entire X chromosome, normal or structurally abnormal, is involved in the formation of the sex chromatin. This view is supported by the observation of an apparently decreased size of the sex chromatin in a patient who was interpreted to have a deletion of part of *the long arm* of the X chromosome (*Jacobs et al.* 1961). Further evidence is obtained from the fact that it is the whole, normal or structurally abnormal, X chromosome that is labelled with ^{3}H-thymidine late in the DNA synthesising period, and that one heteropyknotic chromosome has been observed in cells in early prophase from normal human females (*Ohno* 1963).

In addition, all patients in the present work who were sex chromatin negative were considered to have XO cells, and none was found to be sex chromatin positive and to have only 45 chromosomes and a supposed

XO karyotype. Apparent exceptions to the rule that sex chromatin positive cells have more than one normal X chromosome have been reported in two sex chromatin positive patients with ovarian dysgenesis and an apparent XO constitution (*Grumbach et al.* 1960, *Jacobs et al.* 1961) and in a sex chromatin negative male pseudohermaphrodite with an apparent XX/XY/XO constitution (*Schuster* & *Motulsky* 1962). One of the patients with ovarian dysgenesis later turned out to be a mosaic with an XO/XX/XXX constitution (*Grumbach* & *Morishima* 1962). It was claimed that XO cells derived from this case might be sex chromatin positive and have a late labelling X chromosome (*Morishima et al.* 1962). The above findings may be explained on the basis of the mosaicism and of the technical difficulties (pp. 39), but other explanations cannot be excluded at present. It should also be mentioned that the patient with one, apparently "enlarged X chromosome" and a male phenotype reported by *Elves* & *Israëls* (1962) was sex chromatin negative.

Origin of the chromosome aberrations

Theoretically the chromosome abnormalities described here may originate either during the maternal and/or the paternal gametogenesis or in the embryogenesis. The latter is the case in mosaicism but, on the other hand, the initial karyotype of the zygote is then unknown. Future studies on human meiosis might to some extent help to clarify these problems.

On the other hand, it is possible by the use of sex-linked genes to investigate whether an X chromosome is paternal or maternal. This problem has been approached in the present work by studying the occurrence of colour-blindness and the blood group Xg in the patients and their parents (pp. 42).

On the basis of such studies it was decided that, in the present material, nine out of eleven patients with an *XO constitution* had received the maternal, and two the paternal X chromosome. This does not of course necessarily imply that the abnormal division giving rise to the XO zygote occurred during the gametogenesis, since other cell types might have been eliminated at an early stage during embryogenesis or might have remained undetected. If the abnormal division occurred equally often in either gametogenesis one would expect to find twice as many XO individuals with the maternal X chromosome than with the paternal one.

The result obtained here, i.e. nine with the maternal and two with the paternal X chromosome, did not differ significantly from this theoretical value. Similar findings, including those of the present material, were recently described by *Lindsten et al.* (1963 *c*). Earlier publications regarding

these and other sex-linked genes in patients with Turner's syndrome consist mainly of reports of single cases. The X chromosome has then been considered to be of maternal and more rarely of paternal origin (see *Lindsten et al.* 1963 *c*). Studies of larger groups are required before definite conclusions can be drawn regarding the frequency of maternal and paternal X chromosomes in patients with Turner's syndrome and an XO constitution.

It should also be mentioned that the two patients with an XO constitution in the present material who, on the basis of colour-blindness and the blood group Xg, were considered to have the paternal X chromosome, were sex chromatin negative. These findings disagree with the theory of *Muldal* (1962) which proposes that patients with Turner's syndrome and an XO constitution should always have the maternal X, and that those with the paternal X, if compatible with life, should be sex chromatin positive.

Evidence obtained in the present work indicates that the *iso-chromosome for the long arm of X,* was of paternal origin in one case. This interpretation was based on the informative segregation of the genes for deutan colour-blindness and the blood group Xg in this family (pp. 42). It had to be assumed that the aberrant chromosome found in the patient was a true iso-chromosome, and that the original zygote did not have an XO constitution which had undergone numerical and structural aberrations during embryogenesis.

If the above interpretations are correct the segregation of these genes in the same family gives the genetic information that the genes for deutan color-blindness and the blood group Xg might be located on the short arm of the X chromosome.

In this connection the hypothesis proposed by *Lyon* (1961) has to be taken into consideration. This hypothesis, based on findings obtained in the mouse, proposes that one of the X chromosomes in cells from normal females is genetically "inactive". The other X chromosome, and the only one in cells from normal males, is considered "active". The "inactivation" should occur at random in each cell in early embryogenesis, and the "inactive" X chromosome was considered to be heteropyknotic and form the sex chromatin. The Lyon hypothesis has been applied also to man (see e.g. *McKusick* 1962). The heteropyknosis of one of the X chromosomes in cells in prophase, and the late synthesis of DNA by one of the X chromosomes in cells from normal females, has been considered to support this hypothesis. However, it still remains to be shown that heteropyknosis and late DNA synthesis also mean genetic "inactivity".

Since the two types of structurally abnormal X chromosomes studied with regard to DNA synthesis also synthesised their DNA late, it cannot

yet be evaluated whether they should be considered "active". It is possible that the "active" X chromosome has to be intact, and therefore it cannot be judged whether these findings disprove the Lyon hypothesis.

On the basis of the studies on the blood group Xg in the families of patients with presumptive iso-chromosomes in the present material the following conclusions may be drawn. If the iso-chromosomes were "inactive", they would be of paternal origin in four cases irrespective of the location of Xg on the X chromosome. On the other hand, if the iso-chromosomes were "active", a paternal origin would require that Xg is located on the short arm of X. In no case was evidence obtained for a maternal origin of the iso-chromosomes. These findings have recently been reported elsewhere by the author (*Lindsten et al.* 1963 *a, b*).

The origin of the other two types of structural aberrations of the X chromosome observed in the present work, the *ring chromosome* and the *deletion of the short arm,* could not be decided since the segregation of the blood group Xg was not informative, and colour-blindness was not found in the two families. Furthermore, testicular biopsies from the fathers of the patients could not be obtained.

As mentioned above it is not known where the structural aberrations of the X chromosome arise. They may arise in the zygote, spontaneously or after X-ray irradiation, but a more useful approach is to think of a meiotic origin of those structural aberrations which cause a more or less characteristic clinical picture. The meiotic origin is supported by the fact that the X and Y chromosomes are heteropyknotic, and sometimes appearing as univalents at diakinesis in the male meiosis (*Ford & Hamerton* 1956). It is known that univalents might form iso-chromosomes (*Sears* 1952). In contrast, the two X chromosomes in the female are isopyknotic during meiosis, and therefore might be less likely to undergo aberrations.

Further evidence supporting a meiotic origin in the fathers of the patients has been obtained in the present work both for the iso-chromosomes and the XO constitution. A deficiency of females among the sibs of the patients was found in both these groups. It could not be evaluated whether this is true also for the XO/XX group because of the small number of cases with this chromosome constitution. This abnormal sex ratio with a relatively increased number of males indicates a disturbed paternal meiosis and, therefore, a probable paternal origin of the abnormal chromosome constitutions. It might then be questioned, whether increased paternal age could influence the occurrence of these abnormalities. The paternal age in the present material was, however, within normal limits.

On the other hand, two XO patients had the paternal X chromosome, indicating a maternal origin of the abnormal chromosome constitution. The maternal age at the birth of the patients and the birth order of the

patients were normal in the present material. On the other hand, the maternal age has been increased in other conditions connected with chromosome abnormalities, e.g. in mongolism (*Penrose* 1933), but not in all the cytogenetically different types of this disease (*Penrose* 1962). Also in Klinefelter's syndrome the maternal age may be increased, and may eventually show a bimodal distribution (*Penrose* 1961, *Lenz* 1959).

The observed deficiency of females among sibs of some groups of patients with Turner's syndrome and different chromosome abnormalities might eventually be explained on the basis of a specific genetic mechanism analogous to the "segregation-distortion" type of meiotic drive described by *Sandler et al.* (1959) in *Drosophila melanogaster*. This question cannot be solved at present. Further studies are required in Turner's syndrome and in other conditions associated with chromosome abnormalities in order to elucidate the problem of specific genetic factors in the aetiology of chromosome abnormalities.

Further observations on the occurrence of Turner's syndrome

There are a few findings concerning the patients in the present work which may prove to be of genetical importance, although their significance cannot be fully appreciated at present.

There was an apparent increase in the number of twins in the families of the patients with Turner's syndrome presented here. This increase was most evident in the iso-chromosome group but was also found in the XO group. No deviation was, however, found between the observed and the expected number of twin pairs of unlike sex and twin pairs of like sex. It should be mentioned in this connection that patients with Turner's syndrome on rare occasions have been twins (*Frasier et al.* 1961, *Turner & Zanartu* 1962). Furthermore, two instances have been reported in which a patient with Turner's syndrome and an XO constitution had a "monozygotic" twin brother with an apparently normal male karyotype (*Turpin et al.* 1961, *Edwards et al.* 1963). In addition, "gonadal dysgenesis" has been observed in sisters (*Klotz et al.* 1956, *Elliott et al.* 1959, *Izakovič* 1960).

Sibs of patients with Turner's syndrome have on rare occasions been reported to have Klinefelter's syndrome (*Bassøe* 1956), trisomy in the group 13–15 (*Therman et al.* 1961) and mongolism (*Johnston* 1962). In the present material, by interviews of the patients and/or their parents, no conditions known to be associated with chromosome abnormalities could be demonstrated in the families.

Consanguinity was recorded in one case in the present material, and has earlier been reported in a few more cases (see *Haddad & Wilkins* 1959). These frequencies are based on too small a series to be evaluated.

The fact that most patients with Turner's syndrome are sex chromatin negative has made it possible to study the frequency of this disease in large populations of newborn children. Thus, *Court Brown* (1962) reported that the number of XO individuals was 0.4/1000 live female births in a Scottish material of more than 20,000 children studied. This frequency is very different from the one which might be expected on theoretical grounds, and which assumes that an abnormal division giving rise to an XO constitution occurs equally in both the male and female gametogenesis. According to these calculations XO patients should be more common than those with an XXY sex chromosome constitution (*Twiesselmann et al.* 1962). However, the frequency of the latter is 1.7/1000 live births (*Court Brown* 1962).

The importance of the apparently increased frequency of twins in the families of patients with Turner's syndrome, and the comparatively low frequency in the population of at least those patients with an XO constitution, in the aetiology of the disease cannot yet be evaluated.

Some clinical findings

Since most of the clinical and laboratory observations in the present study were used mainly as a basis for selection of the patients, the discussion will be limited to only some of them, and to some problems of special interest from a genetic point of view.

Perceptive hearing impairment.—In the present material 20 out of 41 patients studied had a pure perceptive hearing impairment, mostly consisting of a "dip" in the audiogram. The parents of four of the patients did not show defects of hearing similar to those found in the patients. No exogenous causes of this type of abnormality are known or could be demonstrated in the present material.

It may be of special interest to note that the types of perceptive hearing impairment observed here are similar to some of those considered to be hereditary. Furthermore, there is a clear predominance of males affected in this heritable group, and only the mothers of these males have shown hearing impairment (*Wedenberg,* in preparation). These findings tend to indicate a sex-linked inheritance of certain types of perceptive hearing impairment. X-linked congenital and progressive deafness has earlier been reported by several authors (review in *McKusick* 1962).

The frequency of perceptive hearing impairment in a normal Swedish population of children of about 14 years of age was 4.5 per cent in boys and 2.4 per cent in girls (*Wedenberg,* personal communication). Unless there is no special genetic mechanism acting, the high frequency of hearing impairment of hereditary type in Turner's syndrome is difficult to explain on a pure gene basis. An alternative explanation would be that the hearing

impairment is caused by a "malformation" of unspecific aetiology. Further studies are required to elucidate this problem.

Physical growth.—The short stature is an obligatory sign in patients with Turner's syndrome. Two of the possible aetiological factors for this short stature, i.e. a defect in the epiphyseal zones and an abnormal endogenous growth hormone, have recently been discussed in detail by the author as a result of the finding of an altered, generally increased, growth hormone-like activity in serum from these patients (*Almqvist et al.* 1963). The first hypothesis is supported by the finding of generalised skeletal abnormalities in X-ray examinations, mainly a dysplastic bone structure and abnormal epiphyseal zones. Administration of human growth hormone in short-term studies induced a nitrogen retention in patients with Turner's syndrome (*Forbes et al.* 1962). Whether this means that these patients will also grow during treatment with human growth hormone remains to be shown.

The growth curves of many of the patients in the present material have been included in order to demonstrate the growth pattern of patients with Turner's syndrome. It is evident from these curves that the growth rate is retarded and the patients pass the lower 3σ limit for normal variation of height at different ages. No information was generally available before six to seven years of age. Furthermore, oestrogen therapy did not change the slope of these growth curves remarkably.

It might also be questioned whether patients with Turner's syndrome are already small at birth, an opinion which has been supported by several authors (*Haddad & Wilkins* 1959, *Polani* 1961). In the present material the mean birth weight was significantly decreased. There were no differences between patients with different sex chromosome constitutions. Furthermore, the duration of pregnancy was significantly shorter than normal.

A comparison between groups of patients with Turner's syndrome with different sex chromosome constitutions

A study of the clinical differences between patients with Turner's syndrome with different chromosome abnormalities might be of significance for the localisation of different genes on the chromosomes, and might also give information regarding the nature of the chromosome abnormalities. Findings concerning sex-linked genes in connection with sex chromosome aberrations are obvious examples (see pp. 42 and 70). On the other hand, the parameters generally used for the comparison of patients with ovarian dysgenesis (malformations, physical growth etc.) are unspecific, and probably the result of a genetic imbalance caused by the abnormal sex chro-

mosome constitution rather than the manifestation of single genes located on the X chromosome. One exception might be the hearing impairment discussed above.

A comparison firstly between the present case material and apparently normal women, and secondly between groups of patients with Turner's syndrome and different sex chromosome constitutions is difficult, since the case material was selected on the basis of a specific clinical picture in females who generally had passed the "puberal" years. It is also difficult to compare the present material with others reported earlier, since those which were most carefully studied from the clinical point of view were not cytogenetically analysed. On the other hand, the cytogenetically analysed materials consist mainly of reports of single cases often very briefly described clinically. The absence of clearcut definitions of the parameters used for comparisons is evident, and subjective errors have therefore been introduced. A typical example is the height of the palate arch which was normal in the present material but which has earlier been considered to be increased (pp. 55). Normal values for some of the parameters commonly used, e.g. body height, are often lacking or have been omitted.

Furthermore, the possibility of mosaicism should always be considered even if it cannot be proved. It is also very difficult to draw any conclusions from comparison between cases with mosaicism, since generally the distribution of the mosaicism is unknown. The hypothesis of the "inactive" X chromosome (*Lyon* 1961) must also be taken into account together with the finding in the present work that the structurally abnormal X chromosomes always synthesised DNA late in the synthesising period, in analogy with one of the X chromosomes in cells from normal females. If this means genetic "inactivity" one would not expect to find great differences between the different groups of patients. On the other hand, if the structurally abnormal X chromosomes are genetically "active", clinical differences might be expected.

A few parameters regarding possible clinical differences between groups of patients in the present material will be discussed in the following.

Malformation.—Because of the manner of selecting the patients for the present study one would *a priori* not expect to find great differences between the groups of patients. This was in fact the case, and no striking discrepancies were observed between groups in external or radiologically studied malformations, but the variation within each group was great. Some variations between groups were however noted: webbing of the neck, epicanthic folds, localised oedema of the feet at birth, and coarctation of the aorta were almost exclusively found in patients of the XO group, and none of these patients had an iso-chromosome. Similar findings have been reported by *de la Chapelle* (1962). Webbing of the neck in a patient

with an iso-chromosome was, on the other hand, described by *Hamerton et al.* (1962). Whether the XO constitution might cause more severe malformations than the other abnormalities cannot be evaluated at present.

Physical growth.—There were no significant differences in body height between groups of patients having different chromosome constitutions and closed epiphyseal zones. The variation was great within each group. However, there was a tendency for the patients of the XO/XX group to be somewhat taller, especially if those with closing epiphyseal zones were included. The same tendency in a few other cases with this mosaicism has been reported by *Ferrier et al.* (1962) and *de la Chapelle* (1962). Patients with ovarian dysgenesis and an XY, XX or XO/XX/XXX are generally of normal height (*Harnden & Stewart* 1959, *Hauser et al.* 1960, *Carr et al.* 1962).

In the present material only one out of the six cases showing some development of the secondary sex characteristics before oestrogen treatment had an XO constitution. On the other hand, the only fertile case so far reported in the literature had this aberration (*Bahner et al.* 1960).

The selection of the patients as discussed above and the small number of cases do not permit any definite conclusions, but indicate that differences in physical growth might exist between groups of patients with Turner's syndrome and different sex chromosome constitutions.

Intelligence level.—Patients with Turner's syndrome are only rarely found at institutions for the mentally deficient (*Maclean et al.* 1962, *Hamerton et al.* 1962), in contrast to many of the patients with Klinefelter's syndrome and of the triple-X females (*Ferguson–Smith* 1958, *Frasel et al.* 1960). Severely mentally retarded patients with "ovarian dysgenesis" were observed in the material of *Haddad & Wilkins* (1959), but most of their patients had an apparently normal intelligence quotient. This was also the case in the material of *Hampson et al.* (1955).

There was only a slight difference in the mean IQ levels of the present case material and that of the standardisation groups for the tests. A clear tendency to a bimodal distribution with a peak at a lower intelligence level was found in the XO group of patients. A similar bimodal tendency can be seen in the material of *Hampson et al.* (1955). The patients with an iso-chromosome or an XO/XX constitution generally had an IQ of 100 or more. Two of the three patients with these constitutions, who could not be tested, both had an academic education. On the other hand, *Hamerton et al.* (1962) found one patient with an iso-chromosome among mentally defectives.

These findings support the view that there might exist some clinical differences between groups of patients with Turner's syndrome with an XO constitution on the one hand, and with other constitutions on the other.

However, it is evident from the above discussion that larger groups of patients with different sex chromosome constitution must be studied before definite conclusions can be drawn. Furthermore, as mentioned in the introduction, those pathological conditions with similar chromosome abnormalities as patients with Turner's syndrome but a different clinical picture, should be taken into consideration. A study of a material consisting of newborn children or of patients selected on cytogenetical and not on clinical criteria should give a better knowledge of the role of the various chromosome abnormalities in ovarian dysgenesis.

SUMMARY

The present work on aberrations of the X chromosome in man is based on a study of 57 patients with Turner's syndrome according to the definition used by the author, i.e. a clinical entity composed of short stature, symptoms of ovarian dysgenesis, and different types of malformations other than short stature and ovarian dysgenesis.

Various types of numerical and/or structural aberrations of the X chromosome were demonstrated in all patients except for one with an apparently normal female karyotype.

The numerical aberrations of the X chromosome include the originally described XO and XO/XX constitutions, here observed in 35 and seven respectively, of the 57 patients. The most common structural aberration was the presumptive iso-chromosome for the long arm of X, originally described by the author, and found in 11 of the patients. In one patient, another new type of structural aberration was described, a ring chromosome of X. Furthermore, a deletion of the short arm of X was verified as an abnormality in one case.

It appears that mosaicism is very common in cases with structural aberrations of X, since it was demonstrated in all patients in this group except for two out of the 11 cases with presumptive iso-chromosomes. In one case the type of mosaicism could not be definitely determined.

Evidence for the identity of the above structural aberrations was obtained partly from morphological criteria, partly from studies of the area of the sex chromatin and nuclei as well as their DNA content, and from ^{3}H-thymidine labelling of the DNA synthesis of these chromosomes. The morphological criteria of relative length, position of the centromere and shape were used for the initial classification of the aberrations. The area and the DNA content of the sex chromatin, in comparison with these properties of the sex chromatin in cells from normal women, were apparently increased in cells with presumptive iso-chromosomes, and decreased in cells with deletion of the short arm of X. Furthermore, in analogy with one of the X chromosomes in cells from normal females, the structurally abnormal X chromosomes, i.e. the iso-chromosome and the ring chromosome, were labelled late in the DNA synthesising period. The normal X chromosome in the latter cells did not show this behaviour. Finally, the iso-chromosomes were symmetrically labelled along their whole length.

These findings demonstrate that the above structurally altered chromosomes were X chromosomes, and that probably the whole of one X chromosome constitutes the sex chromatin.

Studies on the sex-linked genes for deutan colour-blindness and the blood group Xg in patients with the XO constitution and their parents, revealed that the single X chromosome may be of either paternal or maternal origin.

There were indications from studies of the above sex-linked genes that in some cases the iso-chromosomes could be of paternal origin, and that these genes are located on the short arm of the X chromosome.

Studies of the pedigrees of the patients revealed an apparent increase in twin births in the families of the patients, and a deficiency of females in the sibships of patients with iso-chromosomes and in those with an XO constitution.

The results of the clinical and laboratory investigations of the patients are presented in detail. From the findings it may be mentioned that about 50 per cent of the patients had pure perceptive hearing impairment similar to that considered to be hereditary, 20 per cent had other types of hearing impairment. The mean intelligence quotient of the whole material was slightly below the value 100, and bimodally distributed with a peak at a lower intelligence level in the XO group.

Special attention has been given to data regarding physical growth, including growth curves for individual patients, assays of growth hormone-like activity of serum, and radiological studies of skeletal structure and epiphyseal zones.

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APPENDIX

Case reports

General

In the following, a short report is given of each patient. The sex chromosome constitution of each subject is recorded after the date of birth. Some of the cases have been reported earlier, and for these the references are given.

Pedigrees are presented in three cases. The following symbols are used: ○ = female; □ = male; • = spontaneous abortion; † = dead. In the cases where information could be obtained, the pregnancies and deliveries were normal, and there was no evidence of irradiation treatment or of X-ray examination of the abdominal organs during the mother's pregnancy. Most of the patients had had common childhood diseases without complications. Only three patients had had skeletal fractures, and these will be discussed separately. There were in the families no incidence of short stature (except in Case 44) or evidence of diseases known to be connected with chromosome abnormalities. Only in Case 3 was consanguinity registered.

Where applicable, the levels of education reached by the patients are given. Since the organisation of the school system in Sweden is somewhat different from that of many other countries, a brief description of the terms used follows.

"Folkskola": an eight or nine year elementary school, including both primary and upper secondary school levels and receiving pupils at the age of about seven years.

"Realskola": a lower secondary school attended for three, four or five years after the fourth year of "folkskola", depending on which of several possible systems of education is being followed, and catering for pupils between 11 and 16 or 17 years of age.

"Flickskola": a lower secondary school ("realskola") for girls.

"Gymnasium": an upper secondary school attended for three to four years and leading to matriculation.

"Folkhögskola": an adult continuation school. A two to three year secondary school, often residential and co-educational and attended mostly by young adults, and offering a wide range of subjects and courses to those desiring further education after "folkskola" or "realskola" levels, but not wishing to attend "gymnasium" or the university.

Case 1. M.G., born July 12, 1961. *XO.* Previously reported by *Almqvist et al.* (1963).

The diagnosis of Turner's syndrome was made at birth, and based on the appearance of broad skin folds on the back of the neck together with localised scleroedema of hands, feet and the lateral parts of the lower legs. There was no evidence of disease of heart or kidneys. The oedema of the hands had disappeared spontaneously at the age of one and a half months, but that of the feet and lower legs persisted, but was less pronounced, at the age of seven months. There was luxation of the left and subluxation of the right hip joint, but these anomalies disappeared spontaneously at the age of seven months. The gain in body weight was slow during the first six months of life, when the patient suffered from several severe infections of the throat. After the age of six months the mental and physical development was accelerated. At the last examination, at seven and a half months of age, the electrocardiogram showed signs of hypertrophy of the left ventricle. There was, however, no evidence of coarctation of the aorta.

Case 2. S.B., born February 21, 1961. *XO.* Fig. 13. Previously reported by *Almqvist et al.* (1963).

At birth the patient had localised oedema covering the feet, the anterior parts of the lower legs and the backs of the hands. There was no evidence of disease of heart or kidneys. The oedema of the hands had disappeared at the age of one month, and that of the feet at the age of two months. For a short period when she was one month old, the girl had clonic contractions of the arms. A spinal puncture gave normal findings, and several electroencephalograms were apparently normal. Total serum protein was low at one determination (4.6 g/100 ml) and normal at another (5.4 g/100 ml). The patient was successfully operated on for pyloric stenosis at the age of two months. Up to this time she had developed normally both mentally and physically.

Her mental and physical development after the operation was apparently normal up to the last examination at seven and a half months.

Case 3. H.G., born May 25, 1961. *XO.* Previously reported by *Almqvist et al.* (1963).

Turner's syndrome was suspected at the age of two months because of localised oedema of the feet. This disappeared spontaneously at the age of five and a half months. The patient had also had oedema of the hands at birth, but it disappeared spontaneously before two months of age. There were no signs of heart or kidney diseases but two low (4.7 and 5.1 g/100 ml) values for total serum protein were found. Her physical and mental devel-

opment was apparently normal. Histological examination of a skin biopsy from the oedematous parts of the feet revealed in the epidermis a coarser than normal structure and decreased birefringence of the collagen fibres. The elastin threads, sweat glands, sebaceous glands, hair, smooth muscle fibres and blood and lymph vessels were normal. Mast cells were present in apparently normal number. No oedema was visible. The subcutis could not be completely investigated since the biopsy was too small, but collagen and elastin threads were similar to those in the epidermis. There was no oedema, and blood and lymph vessels and adipose tissue were apparently normal.

The father of the patient and his father-in-law were first cousins.

Case 4. M.L., born July 16, 1951. *XO.* Previously reported by *Fraccaro et al.* (1960 *d*).

The diagnosis of Turner's syndrome was suspected at the age of one year and nine months because of short stature (79 cm; lower normal limit 78 cm). Her mental development had been apparently normal, and she had been healthy except for several minor and some severe infections of the throat during childhood. She walked at the age of 15 months. At four years of age she was tonsillectomised and operated on for pharyngeal adenoids. At the age of seven years and six months she had poliomyelitis with slight paralysis of the muscles of the legs and abdomen. At the age of seven years and 11 months, when the diagnosis of Turner's syndrome was made and the XO sex chromosome constitution was found, she seemed to have recovered completely.

She was in her fifth year at school and in a normal grade. There had been discussion as to whether she should be placed in a special class for backward children.

Case 5. I.B.J., born June 26, 1946. *XO.* Fig. 18 *d.*

The diagnosis of "elephantiasis" was made at birth when she was hospitalized and at the age of five months, because of non-pitting oedema on the back of the hands and feet. Histological examination of a skin biopsy taken at the age of three years revealed in the epidermis, a normal structure of the collagen fibres with normal birefringence, probably an increased amount of elastin threads and no oedema. The blood vessels, smooth muscle fibres, hair, sebaceous and sweat glands were normal. The lymph vessels were dilated, and mast cells were present. In the subcutis the collagen structure was in some parts coarser with decreased birefringence. The elastin was as in the epidermis. There was obvious oedema, an increased number of lymph vessels partly dilated, and normal blood vessels and adipose tissue. The oedema disappeared very slowly and, at

the age of 16 years, it still persisted on the back of the right foot and to a very slight degree on the back of the first and second phalanges of the fingers (Fig. 19 *a*).

She also sought medical advice at the age of 12 and 16 years because of short stature, and the last time also because of primary amenorrhea.

The patient had always been healthy and had an apparently normal mental development. She was about to finish lower secondary school (realskola).

Case 6. I.M.L., born September 4, 1946. *XO.*

After birth the patient increased slowly in weight. The mother noted that she was physically underdeveloped at the age of eight months. She walked at 18 months of age. She had always been considered a healthy child except for short stature. Her mental development was apparently normal.

The patient had consulted physicians on several occasions during childhood because of her short stature. The diagnosis of Turner's syndrome was first made when she was referred to a paediatrician at the age of 16 years and was based on her short stature and primary amenorrhea. She also had at that time a moderate iron deficiency anaemia.

She had just finished elementary school (folkskola).

Case 7. M.B., born June 2, 1945. *XO.* Fig. 14 *a.*

The patient's mental and physical development had been slow, and she did not walk until two years of age. Because of hyperflexible joints she had to use braces.

The patient had been obese since the age of five or six years. She had been hospitalized several times since the age of nine years, because of obesity, short stature and later, primary amenorrhea. At the age of 16 years, when the diagnosis of Turner's syndrome was made, she still had nocturnal enuresis. An exploratory laparotomy revealed a hypoplastic uterus and Fallopian tubes, and only "streaks" were found at the sites of the ovaries. Histological examinations of the "streaks" showed only connective tissue with groups of polygonal cells of Leydig type,[1] sometimes containing Reinke's crystalloids (Fig. 20 *a, e, f*). No follicles or corpora lutea

[1] The large, polygonal cells usually found in connection wiht nerves within the hilar region of normal ovaries are mostly called the "hilar cells" or the "Leydig cells of the ovary" while the finding of cells of similar appearance embedded in the ovarian stroma is generally described as "diffuse stromal luteinisation" or "thecomatosis". There is no clear distinction between the cells in these two locations except that Reinke's crystalloids are found only in the "hilar cells". Therefore, in the present work, the large, bright and more or less polygonal cells found in the ovarian stroma or in the hilar tissue are referred to as "cells of Leydig type".

but some mesonephric ducts were found in the hilar region (Fig. 20 *c*). Furthermore, there was one tubule of unusual type, more like an undifferentiated testicular tubule than the mesonephric tubules generally found (Fig. 20 *d*).

Because of her mental retardation the patient started school one year later than normal, and was referred to a special class. She was still at a school for mentally retarded children at the last examination.

Case 8. I.B.H., born May 3, 1941. *XO*. Previously reported by *Fraccaro et al.* (1960 *a*).

The patient had always been healthy except for a short stature. Her mental development was apparently normal.

She first sought medical advice at the age of 12 years because of her short stature and later also because of primary amenorrhea.

Laparotomy at the age of 18 revealed a small, flat uterus and underdeveloped Fallopian tubes. At the sites of the ovaries only fibrous "streaks" were found. Histological investigations of the "streaks" showed a thin tunica albuginea and a stroma of ovarian type, but no follicles or corpora lutea. Towards the hilus, there were groups of cells of Leydig type, sometimes arranged like alveoli, but without Reinke's crystalloids. Furthermore, groups of mesonephric ducts and a few single rudimentary mesonephric tubules were observed in the hilar region.

When last seen, at the age of 18, the patient had finished elementary school (folkskola) and an adult continuation school (folkhögskola).

Case 9. V.G., born June 16, 1944. *XO*. Previously reported by *Fraccaro et al.* (1960 *c*).

The patient was admitted to a paediatric clinic at the age of nine months because of rickets, slow gain in weight and persisting non-pitting oedema of the feet. Oedema on both the hands and the feet was observed at birth. This disappeared spontaneously at the age of two to three months. There were no signs of disease of the heart or kidneys. At the time of admission she also had a retarded skeletal age and was therefore treated with thyroid extract for a least three months. She was considered to have skeletal changes similar to those found in rickets.

Her mental development was apparently normal.

At the age of 11 years and nine months she was hospitalized because of infections of the ears.

The diagnosis of Turner's syndrome was made when she again consulted a paediatrician at the age of 15 because of her short stature since early childhood, and primary amenorrhea.

She has been working as a maid for some time.

Case 10. L.J., born July 21, 1944. *XO.* Previously reported by *Almqvist et al.* (1963).

Except for her short stature she had always been healthy and her mental development had been apparently normal. At the age of 13–14 years she was hospitalized because of severe infection of the ears. She consulted a physician at the age of 16 years because of short stature and primary amenorrhea, and the diagnosis of Turner's syndrome was then made.

She has been working as an office girl.

Case 11. M.O., born January 21, 1943. *XO.* Fig. 18 *e.* Previously reported by *Almqvist et al.* (1963).

The right foot, especially the heel, had since birth been intermittently swollen and sometimes discharging. A skin biopsy taken at the age of 18 years revealed a lymphangioma with multiple small cysts. It was not possible to make a radical operation. During childhood she was hospitalized because of several severe ear infections and operated upon a number of times. She had otherwise been healthy except for her short stature, and her mental development had been apparently normal.

She was referred to our clinic at the age of 17 years because of short stature and infantilism.

The patient had been doing domestic work for four years, after having finished elementary school (folkskola) and she had just started at an adult continuation school (folkhögskola).

Case 12. B.G., born October 12, 1943. *XO.*

Her mental development had been apparently normal. She suffered from repeated ear infections, sometimes with suppuration, over a period of three to four years, but was otherwise healthy.

She had always been of short stature and had therefore consulted physicians several times since the age of four years.

The patient was referred to our clinic with the diagnosis of Turner's syndrome at the age of 18 years.

She had finished elementary school (folkskola) and was studying to be a children's nurse.

Case 13. K.A., born December 30, 1943. *XO.* Previously reported by *Almqvist et al.* (1963).

The patient had always been of short stature but had had an apparently normal mental development.

She had during childhood had periods of illness and vomiting lasting one to five days, and for about one year, at 14 years of age, she was depressed and lost about 10 kg in weight. Her skin had always been dry.

She first sought medical advice at the age of 14 because of loss of weight, and nervous anorexia was suspected. Two years later she was referred to our clinic because of short stature and "hypopituitarism". The clinical diagnosis of Turner's syndrome was made at 18 years of age.

She was then in the last year of upper secondary school (gymnasium).

Case 14. L.L., born January 17, 1943. *XO.*

Her father was a German and her mother Norwegian. The patient had always been healthy and had an apparently normal mental development. She had always been of short stature and this had been especially noticeable from 12 or 13 years of age.

She had been consulting a physician since she was 11 years of age because of short stature and infantilism and was referred to a gynaecologist at 15 years of age. The diganosis of Turner's syndrome was then made and an exploratory laparotomy was done. The uterus was considerably underdeveloped and the Fallopian tubes were thin. Only fibrous "streaks" were found at the sites of the ovaries. A histological examination revealed an ovarian stroma-like structure covered by a thin albuginea. Groups of cells of Leydig type without Reinke's crystalloids were found in the hilar region together with some mesonephric remnants. No follicles or corpora lutea were observed.

The patient had finished at a lower secondary school for girls (flickskola) and had recently begun studying to become a secretary (with linguistic qualifications).

Case 15. I.O., born January 18, 1943. *XO.* Fig. 14 *b.*

The patient had always been of short stature but was otherwise healthy, and her mental development had been considered normal.

She sought medical advice several times during childhood, because of short stature and was treated with thyroid extract between two and 11 years of age. She was then referred to our clinic with the diagnosis of "achondroplasia".

The clinical diagnosis of Turner's syndrome was made at the age of 12 years.

She was in the last year of upper secondary school (gymnasium).

Case 16. C.L., born February 20, 1940. *XO.* Previously reported by *Fraccaro et al.* (1960 *a*).

The patient was admitted to a paediatric clinic at the age of five years and 11 months because of her short stature. Her intelligence quotient was 86, tested according to Terman-Merill. Her height was 98 cm (lower normal limit 102 cm). Otherwise she had had an apparently normal mental

development and had been healthy. She had probably been treated with thyroid extract for a short period.

At the age of 19 years she was admitted to a gynaecological clinic because of primary amenorrhea, and the diagnosis of Turner's syndrome was made.

The patient had finished elementary school (folkskola) and was, at the last examination, at an adult continuation school (folkhögskola).

Case 17. B.H., born January 12, 1941. *XO.* Previously reported by *Fraccaro et al.* (1959) and *Fraccaro et al.* (1960 *c*).

The patient had been of short stature since at least the age of three years. Her mental development had been considered normal, and her physical health had always been excellent.

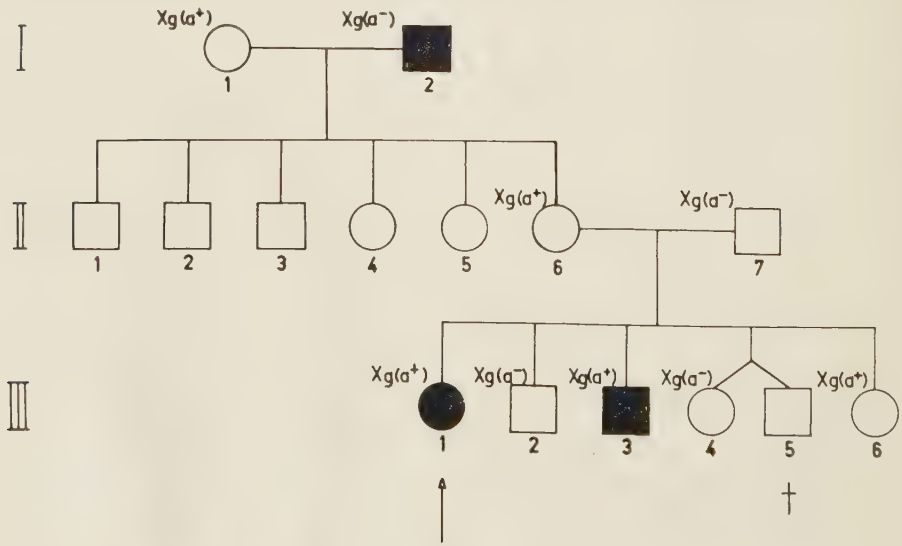
The diagnosis of Turner's syndrome was made at the age of 13 years when she sought medical advice because of short stature and infantilism.

At laparotomy, performed at 14 years of age, markedly underdeveloped uterus and Fallopian tubes were found. Only fibrous "streaks" were found at the sites of the ovaries, and at microscopic investigation only vascularised connective tissue without follicles was observed.

She had finished elementary school (folkskola) and an adult continuation school (folkhögskola) and was working as an office girl.

Case 18. I.L., born September 21, 1941. *XO.* Previously reported by *Almqvist et al.* (1963).

The patient had always been considered a healthy girl with normal mental development. She consulted a physician at the age of 17 because



of infantilism and short stature. The clinical diagnosis of Turner's syndrome was made at the age of 18 years.

Colour-blindness was distributed in the family according to the pedigree above.

The solid black symbols represent colour-blind individuals. The arrow points at the proposita. The individuals III_4 and III_5 were twins. The results of Xg blood group investigations are included in the pedigree to the left of the symbols.

She had finished elementary school (folkskola), and was working as a shop assistant.

Case 19. K.S., born September 1, 1940. *XO.* Previously reported by *Fraccaro et al.* (1959) and *Fraccaro et al.* (1960 *c*).

During childhood the patient had always been healthy except for one attack of pneumonia, for which she was hospitalized. She had always been rather obese and of an obviously short stature.

The patient consulted a paediatrician at the age of 18 years because of primary amenorrhea, and the diagnosis of Turner's syndrome was made.

She had passed through lower secondary school for girls (flickskola) and was a student nurse.

Case 20. B.L., born November 21, 1940. *XO.*

The patient had always been healthy as a child, and her mental development had been apparently normal. She had always been of short stature.

She was referred to our clinic at the age of 16 years because of short stature and primary amenorrhea, and the diagnosis of Turner's syndrome was made. The patient lacked the second, right, permanent incisor of the upper jaw. No further cases with this malformation were known in the family.

She was treated with androgens together with oestrogens between 16 and 18 years of age. No effects, except those found when only oestrogens are used, were observed. At 22 years of age she had an accident which resulted in a fissure in one of the bones of the left ankle.

The patient had finished upper secondary school (gymnasium) and was studying to become a teacher.

Case 21. D.F., born February 18, 1939. *XO.*

The patient was hospitalized at the age of eight months because of a severe bilateral pneumonia, cholera infantum and meningism and one year later because of moderate mental and physical retardation. Her physical development was slow, and she did not walk until the age of two and a half years. Her stature had always been short and this was especially pronounced after 10 years of age.

At the age of 11 years she started to develop a thoracic kyphosis which soon became pronounced.

She sought medical advice at the age of 15 years because of short stature, and the diagnosis of Turner's syndrome was made.

She had finished at a lower secondary school for girls (flickskola) and was working as an office girl.

Case 22. I.H., born September 3, 1938. *XO.* Previously reported by *Almqvist et al.* (1963).

The patient was first hospitalized at the age of one year because of cholera infantum, acute nasopharyngitis and otitis media. At nine years of age she was again hospitalized because of thoracic scoliosis and kyphosis and mental deficiency. There was no evidence of endocrine disorders at this time. Her stature was short from at least six years of age when kyphosis was first noted. The patient sought medical advice at the age of 19 years because of amenorrhea and the fact that she had a gibbus. The clinical diagnosis of Turner's syndrome was made at our clinic when she was 21 years old.

After having finished elementary school (folkskola) she was working as a maid.

Case 23. S.I.H., born January 16, 1938. *XO.* Fig. 14 *c.*

The patient had been of short stature since infancy. Her mental development had been considered normal.

Since the age of two years she had had repeated severe infections of the ears and her right ear had been operated upon at the ages of 15, 20 and 24 years. A cholesteatoma and signs of osteitis were found on the last occasion and a radical operation was carried out. Her hearing had been impaired since 15 years of age and she had for some time been at a school for partially deaf children.

She sought medical advice at the age of 15 years because of amenorrhea and infantilism, and the diagnosis of Turner's syndrome was made one year later.

She had finished lower secondary school (realskola) and was working as an office girl.

Case 24. I.A., born April 16, 1938. *XO.* Fig. 18 *a.*

At the ages of five and seven years the patient had suffered from pyelitis and rheumatic fever. The girl was treated with thyroid extract for obesity and short stature between the ages of 13 and 17 years. No obvious effect was observed on her physical development. She had never reached a spontaneous puberty.

The diagnosis of Turner's syndrome was made at the age of 17 years. The patient had difficulty in following the lessons at school. She had an unskilled job as a storehouse assistant.

Case 25. B.A., born May 28, 1937. *XO.*

After birth the patient increased in weight slowly, because of frequent vomiting and difficulties in feeding. She was hospitalized at the age of 10 months because of pneumonia, bronchitis, purulent otitis media and dyspepsia. At 13 and 17 months she again had periods of vomiting, and up to 13 years headache of migraine type. The mother also had migraine and an organic neuritis. At the age of 13 years she was hospitalized because of rheumatic fever with no definite heart involvement. Her height was then below the lower normal limits.

She was otherwise healthy during childhood, and had an apparently normal mental development.

She sought medical advice at the age of 17 years because of amenorrhea. She menstruated spontaneously somewhat later, but very irregularly and she therefore consulted a gynaecologist at the age of 23 years, at which time the diagnosis of Turner's syndrome was made.

She had passed through upper secondary school (gymnasium) and was working as a secretary with linguistic qualifications. She had been married since 1959 but had no children.

Case 26. B.S–n., born March 17, 1936. *XO.*

The patient was healthy during childhood but of obviously short stature. Her mental development was normal.

She was referred to our clinic at the age of 13 years because of short stature and infantilism, and the diagnosis of Turner's syndrome was made.

She had coarctation of the aorta but refused operation, and still, at the age of 25 years, had no subjective symptoms of heart disease.

She had finished elementary school (folkskola) and was working as an office girl.

Case 27. R.L., born August 4, 1935. *XO.* Fig. 14 *d.*

The short stature was already obvious in early childhood. The mental development had been apparently normal. At the age of 11 years the patient was hospitalized because of acute glomerulonephritis and was said to have had hypertension thereafter.

She sought medical advice at the age of 16 years because of primary amenorrhea. Hysterography at the age of 18 years revealed an underdeveloped uterus and thin Fallopian tubes. The diagnosis of Turner's syndrome was made at this time.

She had finished elementary school (folkskola) and an adult continuation school (folkhögskola) and worked for several years as an office girl. She was married in 1956 but was involuntarily sterile and had recently adopted a child.

Case 28. V.S., born September 5, 1935. *XO.* Previously reported by *Fraccaro et al.* (1960 *a*) and *Almqvist et al.* (1963).

Some of the information given by the patient did not seem to be very reliable and it was found to be impossible to contact her parents.

She was told at the age of 12 years that "there was something wrong with her heart". She had otherwise been healthy.

She sought medical advice at the age of 23 years because of primary amenorrhea. The diagnosis of Turner's syndrome was made at the age of 24 years, partly based on the findings at a laparotomy. The uterus was very small, the Fallopian tubes normal, and only fibrous "streaks" were found at the sites of the ovaries. A histological investigation revealed a stroma of ovarian type and several large groups of large, light cells of Leydig type, sometimes containing crystalloids of Reinke, were found.

The patient had finished elementary school (folkskola) and had been working as a maid for several years.

Case 29. G.A., born July 8, 1934. *XO.*

The patient walked at the age of 16 months. She had always been of rather short stature but was within the normal range of variation of body height up to 12 years of age. At the age of five years she had a severe infection of the right ear followed by impairment of hearing. She had otherwise been healthy.

She consulted a physician at the age of 10 years because of short stature, and since then had been hospitalized seven times for this reason. She had been rather obese since this time.

At the age of 11 years she was treated because of increased lumbar lordosis. She was also treated with thyroid extracts for two short periods of time. The diagnosis of Turner's syndrome was made at the age of 18 years.

The patient had persisting first and second deciduous incisors in the lower jaw. No further cases of this abnormality were known in the family.

For some time she had had difficulties at school, and had to repeat two classes. She was, however, able to finish elementary school (folkskola) and obtained unskilled work as a weaver.

Case 30. G.K., born February 27, 1932. *XO.* Fig. 18 *b.* Previously reported by *Almqvist et al.* (1963).

The patient's physical development had always been slow, and she did not walk until the age of 20 months. Her mental development was apparently normal, and she had always been healthy in other respects.

She sought medical advice at the age of 18 years because of amenorrhea and short stature, and the diagnosis of Turner's syndrome was made two years later.

The patient had finished lower secondary school (flickskola) and was a registered children's nurse. She married in 1957, and had one adoptive child, but no children of her own. Colour-blindness was present in the family. The patient and her father were clearly colour-blind, but not the mother or the sibs.

Case 31. A.F., born November 4, 1932. *XO.* Previously reported by *Almqvist et al.* (1963).

The patient developed slowly and did not walk until two years of age and her primary teeth came late. She was otherwise healthy during childhood. Her dizygotic twin brother had had a completely normal mental and physical development and his height was 175 cm at 29 years of age.

The patient was admitted to our clinic at the age of 18 years because of short stature and primary amenorrhea and the diagnosis of Turner's syndrome was made. Radiological examinations of the carotid artery revealed a cystic anomaly of the occipital lobe and on the left side of the brain. This cyst gave an impression on, but no destruction of, the internal lamina of the occipital bone. There was direct communication between the cyst and the subarachnoidal space, but none between the cyst and the ventricles. No aneurysms were observed.

Only "streaks" of connective tissue were found at the sites of the ovaries at laparotomy. The uterus and Fallopian tubes were considerably hypoplastic. A histological examination showed a stroma of ovarian type with some mesonephric ducts. No follicles or corpora lutea were found.

She had been admitted to a special class for backward children (hjälpklass) at school. After having finished school she had a very simple job as an errand-girl for a few years.

She was prematurely pensioned and lived with her parents.

Case 32. M.N., born December 24, 1932. *XO.* Previously reported by *Almqvist et al.* (1963).

The patient had always been of short stature. Her mental development had been apparently normal. She had several colds and ear infections

during childhood but had otherwise been healthy. The diagnosis of Turner's syndrome was made when she sought medical advice at the ages of 18 and 19 years because of short stature and amenorrhea. At the last examination it was found that she had been gradually losing hair from her head over the last half year but was otherwise healthy.

She had passed through lower secondary school (realskola) and was working as an office girl.

Case 33. M.S.L., born March 27, 1932. *XO.*

By accident she drank sulphuric acid at the age of two years and was therefore hospitalized. The patient was also hospitalized during childhood because of severe infections of the ears, and a bilateral trepanation of the tympanic membrane was performed. Her mental development was apparently normal. She consulted a paediatric clinic at the age of 11 years because of short stature. A treatment with thyroid extract was interrupted after one and a half months because of nervousness.

The patient was referred to our clinic at the age of 16 years because of short stature and infantilism and the diagnosis of Turner's syndrome could be established. One year later an exploratory laparotomy was performed. The uterus was underdeveloped but the Fallopian tubes were apparently normal. Only fibrous "streaks" were found at the sites of the ovaries. A histological investigation was not made. She was also operated upon because of a polyp of the cervix uteri at 27 years of age.

The patient had passed through elementary school (folkskola) and a commercial school. She had been working as an office girl for several years.

Case 34. V.P., born November 26, 1927. *XO.*

The patient was said to have been born six weeks prematurely and was kept in a couveuse for some time. She suffered a fracture of the left forearm at five years of age but was otherwise healthy and had an apparently normal mental development. Her stature had been short since infancy.

The patient consulted our clinic at 22 years of age because of short stature and primary amenorrhea and the diagnosis of Turner's syndrome was made. An exploratory laparotomy at that age revealed a very underdeveloped uterus but apparently normal Fallopian tubes. At the sites of the ovaries there were only fibrous "streaks", which on histological examination were found to contain connective tissue with mesonephric remnants, but no follicles or corpora lutea.

She had finished elementary school (folkskola) and had been working as a storehouse assistant and cleaner for several years. She married at the age of 21 years, but the marriage was involuntarily sterile.

Case 35. I.J., born March 9, 1919. *XO.* Previously reported by *Almqvist et al.* (1963).

The patient had always been healthy and had an apparently normal mental development. Her stature had always been short. She first consulted a physician at the age of 17 years and was then treated with thyroid extract until the age of 42 years without any affect on her physical development.

The patient sought medical advice at the age of 42 years because of periods of vertigo during the previous two months and the diagnosis of Turner's syndrome was made. The blood pressure was high and the heart volume enlarged, 500 ml/m^2 body area. A skeletal biopsy from the iliac crest was performed because of the dysplastic skeletal structure found on X-ray, but no definite pathological changes were observed at the histological examination.

She had finished elementary school (folkskola) and had a simple job as a maid.

Case 36. Y.L., born March 26, 1946. XX_I. Previously reported by *Lindsten et al.* (1963 *b*).

The patient walked late, at the age of two years. She had an apparently normal mental development and had always been healthy except for a few ear infections during childhood. Her stature had always been short and she therefore consulted a physician at three years of age.

At the age of 13 years she had been to several physicians because of short stature and primary amenorrhea and was treated for short periods with Pregnyl^R (Chorionic gonadotrophin) and thyroid extract without any effect. The diagnosis of Turner's syndrome was made at the age of 16 years.

She wanted to begin upper secondary school (gymnasium).

Case 37. G.E., born March 7, 1944. XO/XX_I. Fig. 15 *a, b.* Previously reported by *Almqvist et al.* (1963).

The patient had always been healthy and had an apparently normal mental development. Her stature had been short since infancy. She consulted our clinic at the age of 14 years because of short stature and infantilism and the diganosis of Turner's syndrome was made.

She had finished elementary school (folkskola) and had been working as an office girl for about two years.

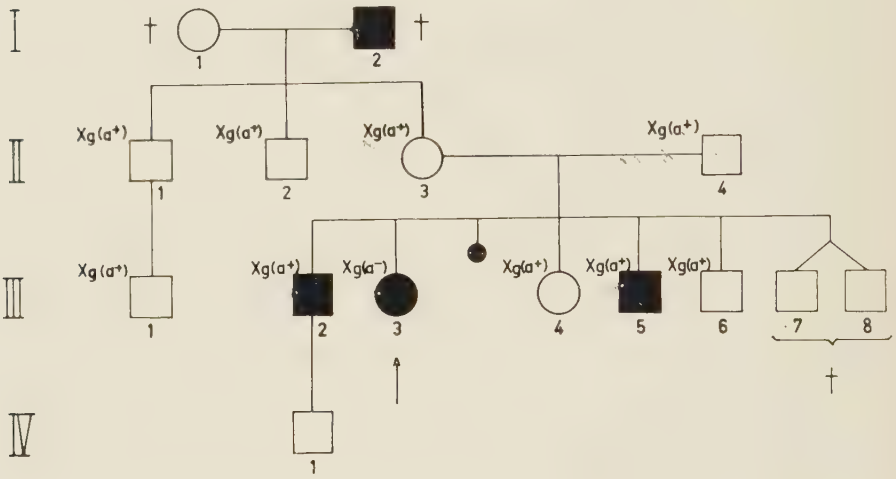
Case 38. B.J., born January 5, 1943. XO/XX_I. Previously reported by *Lindsten* (1961), *Almqvist et al.* (1963) and *Lindsten et al.* (1963 *b, c*).

The patient had always been healthy and had an apparently normal mental development. She had been of short stature since infancy. The

patient was referred to our clinic at the age of 17 years because of short stature, and the diagnosis of Turner's syndrome was made.

She had finished elementary school (folkskola) and was at the time of examination attending an adult continuation school (folkhögskola).

Colour-blindness was distributed in the family according to the following pedigree.



Solid black symbols indicate colour-blind individuals. The arrow points at the proposita. The results of the analysis of the blood group Xg are included to the left of the symbols. The individuals III_7 and III_8 were twins.

The two brothers of the proposita were clearly colour-blind. The Ishihara charts showed that she herself was colour-blind, and she had a normal Raleigh equation but had an increased contrast in the anomaloscope. Identical findings were obtained for both eyes.

Further ophthalmological examinations revealed normal pupil reactions and, except for a slight convergent strabismus on the left side, normal eye movements. Light perception was normal, and the eye fundi had normal maculae. The vessels and papillae were of normal appearance. Visus: 0.9 right; 0.1–0.2 left.

Case 39. B.S., born April 18, 1943. XO/XX_I. Fig. 15 *c*. Previously reported by *Almqvist et al.* (1963).

The patient was cyanotic for a short period after birth and was stimulated with nicethamid and oxygen. She had always been of short stature. Before 15 years of age she had been hospitalized many times because of

severe infections of the ears. The patient had an apparently normal mental development.

The diagnosis of Turner's syndrome was made when she consulted a physician at the age of 16 years because of short stature and primary amenorrhea. At that time she also had chronic eczematous changes of the hands. One year later her right knee was operated on because of a ruptured meniscus.

She had finished elementary school (folkskola) and a two year commercial course and was working as an office girl.

Case 40. A.S., born May 14, 1943. XO/XX_I. Previously reported by *Fraccaro et al.* (1960 *b*), *Almqvist et al.* (1963) and *Lindsten et al.* (1963 *b*).

The patient was referred to our clinic at the age of 14 years because of short stature, and the diagnosis of Turner's syndrome was made. Her stature had always been short and she had an apparently normal mental development. She had always been healthy.

Only "streaks" were found at the sites of the ovaries when an exploratory laparotomy was performed at the age of 17 years. A microscopical investigation of the "streaks" revealed a vascularised stroma without follicles and corpora lutea. The sizes of the uterus and Fallopian tubes were within normal limits but she had then been treated with oestrogens for more than two years.

During the last two years she had albuminuria, probably orthostatic.

She had just finished at a lower secondary school for girls (flickskola) and was working as a physician's secretary.

Case 41. L.A., born September 1, 1942. XO/XX_I. Previously reported by *Fraccaro et al.* (1960 *b*), *Almqvist et al.* (1963) and *Lindsten et al.* (1963 *b*).

The patient was born prematurely, the delivery being sudden and rapid and she was kept in a couveuse for one month. She walked at the age of one and a half years.

Her stature had always been short but she had had an apparently normal mental development and was always healthy during childhood. She was referred to our clinic at the age of 16 years because of short stature, and the diagnosis of Turner's syndrome was made. An exploratory laparotomy at the age of 17 years revealed an underdeveloped uterus and apparently normal Fallopian tubes. Only white fibrous "streaks" were found at the sites of the ovaries. Histological examination of the "streaks" showed stroma of ovarian type, a vascularised hilar region with one group of cells of Leydig type but no follicles or corpora lutea.

Since at least 16 years of age she had had symptoms of a progressive

cerebellar degeneration of hereditary type. The most prominent symptoms were progressive hearing impairment, spontaneous nystagmus, diverging alternating strabismus, scandic talk, ataxia, slight spasticity of the left leg, dysarthria, intention tremor, dysdiadochokinesis, and slight muscular atrophy of the hands. There was no decreased sensibility and no evidence of a brain tumour or muscular disease. At the last examination, the patient was not able to walk without support. There were no further cases with this disease known in the family.

She was successful at school for six to eight years, sometimes the best in her class, and had started at a lower secondary school for girls (flickskola). However, as her cerebellar degeneration progressed, she had difficulty in following her school work. At the last examination she was at a school for the physically handicapped. She was prematurely pensioned.

Case 42. C.S., born September 19, 1942. XO/XX_I.

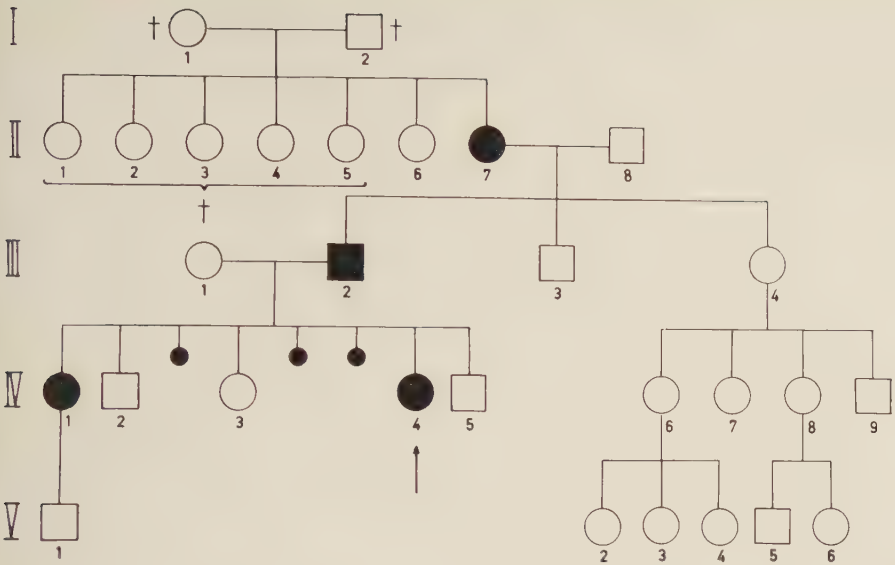
The patient had always been of short stature and had an apparently normal mental development. She was hospitalized for two months at the age of eight months because of diarrhoea. This disappeared spontaneously and she had otherwise always been healthy.

The patient sought medical advice at the age of 10 years because of short stature and thoracic kyphosis and later also because of amenorrhea. At the age of 13 a wedge-shaped compression of the seventh thoracic vertebra occurred and two years later a similar change occurred in the fifth. There was no known trauma on these occasions, but she had a dysplastic skeletal structure. She was treated with thyroid extract and androgens between 15 and 16 years of age without any effect on physical growth.

An exploratory laparotomy at the age of 16 years revealed very underdeveloped uterus and Fallopian tubes. Only fibrous "streaks" were found at the sites of the ovaries. On the left side, however, a yellow formation, some millimeters long, was found, which on histological examination proved to be ectopic adrenal tissue. The zona fasciculata was rather thick, the zona glomerulosa thin and a few medullary cells were also found. The adrenal tissue was surrounded by an ovarian stroma with groups of cells of Leydig type and with ducts of mesonephric origin (Fig. 20 *b, f*). No follicles or corpora lutea were observed.

The patient lacked the second permanent molars in the upper jaw. This malformation had been common in the family for several generations as seen in the pedigree.

The individual II_7 lacked the second molars in the lower jaw, III_2 the first premolars in the lower jaw and IV_1 the second molar on the left side of the upper jaw.



The other individuals were said to have had normal dentition.

The patient had passed through a lower secondary school for girls (flickskola) and was, at the last examination, attending a commercial course.

Case 43. E.S., born September 28, 1938. $XO/XX_I/XX_IX_I$. Fig. 17 *a*.

The patient had been hospitalized several times because of ear infections since the age of two years, and at the last time at 10 years of age, she was operated upon on the right side. Except for eczema she had otherwise been healthy. Her stature had always been short but her mental development was apparently normal. From 10 years of age she had been very obese.

The patient consulted our clinic at the age of 15 years because of short stature, obesity and primary amenorrhea and the diagnosis of Turner's syndrome was made.

She had finished lower secondary school (realskola) and was working as a children's nurse.

Case 44. M.A., born February 19, 1937. XX_I. Previously reported by *Fraccaro et al.* (1960 *b*), *Almqvist et al.* (1963), *Lindsten et al.* (1963 *b*) and *Muldal et al.* (1963).

Her mother developed very slowly, menarche being at 17 years of age, and she was of short stature, height 149 cm (lower normal limit 153.3 cm). The patient was a dizygotic twin and the twin sister had had a completely normal mental and physical development. The sister's height was 161 cm at 24 years of age.

The patient was hospitalized several times during childhood because of ear infections. Her development was slow. She walked at the age of 20 months, and was of short stature, at least from two years of age. She had otherwise been healthy and had an apparently normal mental development.

Before 14 years of age she was treated with thyroid extract for an unknown period of time. No effect on the physical development was noted. Since the age of 14 years, when the diagnosis of Turner's syndrome was made, she had been hospitalized five times because of short stature and later also because of primary amenorrhea.

The patient had passed through elementary school (folkskola) and an adult continuation school (folkhögskola) and was working as an office girl.

Case 45. M.J., born July 27, 1934. XO/XX_I. Previously reported by *Lindsten* (1961).

The patient had always been of short stature but had had an apparently normal mental development and had always been healthy.

She first sought medical advice at the age of eight years because of short stature, and later on because of the short stature and also primary amenorrhea. She was treated with androgens for two years before 16 years of age, but no obvious effect on the physical development was observed. The diagnosis of Turner's syndrome was made at the age of 17 years, when she was referred to our clinic. At the age of 27 years she had had alopecia areata for about one year.

The patient had passed through upper secondary school (gymnasium) and was a Bachelor of Arts working as librarian.

Case 46. R.K., born October 17, 1932. XO/XX_1. Fig. 15 *d*.

Her parents were Finnish. She had always been healthy and had an apparently normal mental development. Her stature had been short since infancy.

The patient first sought medical advice at the age of 15 years because of short stature. The clinical diagnosis of Turner's syndrome was made at 19 years of age, when she again consulted a physician because of the short stature and also primary amenorrhea.

She was treated with androgens for short periods, without any effect on the physical development.

An exploratory laparotomy at the age of 19 years revealed only white fibrous "streaks" (1.5 mm thick × 3 mm broad) at the sites of the ovaries and underdeveloped uterus and Fallopian tubes. Histological examination

of one of the streaks showed irregular, collageneous connective tissue but no follicles and no corpora lutea.

She had passed through upper secondary school to matriculation (gymnasium) and was a Bachelor of Arts working as a librarian.

Case 47. M.C., born March 8, 1944. *XO/XX.* Previously reported by *Almqvist et al.* (1963).

During the patient's childhood there had been a great deal of friction between her parents and she had been hospitalized at the age of five years because of difficulty in sleeping, and at the age of seven years because of nervous abdominal pains. The patient had had an apparently normal mental development. Her stature had always been short. She had been attending a general outpatient clinic fom the age of 12 years because of obesity, severe headaches and sometimes difficulty in sleeping, and later also because of primary amenorrhea. Repeated electroencephalograms at 12 and 13 years of age showed unspecific pathological changes over the central, frontal, and parietal parts of the right hemisphere. These changes were similar to those found in patients with headaches of migraine type. The patient never succeeded in reducing her weight and no organic reason was found for the headaches, which disappeared slowly after a few years.

The clinical diagnosis of Turner's syndrome was made at 17 years of age and was partly based on an exploratory laparotomy which revealed only fibrous "streaks" at the sites of the ovaries and an underdeveloped uterus and Fallopian tubes. Histological examination showed a connective tissue, similar to ovarian stroma, with groups of cells of Leydig type. No follicles or corpora lutea were found.

She was in the second class of upper secondary school (gymnasium).

Case 48. S.S., born March 12, 1942. *XO/XX.* Previously reported by *Fraccaro et al.* (1960 *a*).

The patient increased slowly in weight after birth and was therefore hospitalized at the age of three months. Her stature had always been short but she had an apparently normal mental development and had always been healthy.

The diagnosis of Turner's syndrome was made at the age of 13 years when she first sought medical advice because of short stature and infantilism. Since then she has been hospitalized seven times.

An exploratory laparotomy at the age of 15 years revealed an underdeveloped uterus and apparently normal Fallopian tubes. Only fibrous "streaks" were found at the sites of the ovaries and the "streak" on the left side contained a small cyst. A histological examination was not made.

The patient had finished lower secondary school (realskola). After two

years in upper secondary school (gymnasium) she changed over to a commercial course which she intended to finish.

Case 49. B.N., born April 13, 1944. *XO/XX.* Fig. 16 *a.*

The patient had an apparently normal mental development and had always been healthy. She had been of rather short stature since early childhood.

The diagnosis of Turner's syndrome was made at the age of 18 years when she consulted a gynaecological clinic because of primary amenorrhea.

She had finished elementary school (folkskola) and was working as a barmaid.

Case 50. A.H., born March 2, 1942. *XO/XX.* Fig. 16 *b.*

The patient was hospitalized at the age of 13 years because of a pyelitis but had otherwise been healthy. During the first years at school she was of about the same height as her classmates but later became relatively shorter than they. She had an apparently normal mental development.

She sought medical advice at the age of 15 years because of primary amenorrhea, and the diagnosis of Turner's syndrome was made two years later.

The patient had passed through lower secondary school for girls (flickskola) and was working as an office girl.

Case 51. M.H., born June 18, 1939. *XO/XX.* Fig. 16 *c.*

The patient had always been healthy and had an apparently normal mental development. She had a short stature which was especially noticeable after 12 years of age. At that age the secondary sex characteristics were normally developed. However, only four or five spontaneous menstruations occurred, two years later.

The patient consulted our clinic at the age of 17 years because of short stature and menstrual disorder and the diagnosis of Turner's syndrome was made.

The patient lacked the second permanent incisors of the upper jaw. Her mother was said also to have had this malformation. Several more distant relatives might also have had it, but this was impossible to ascertain.

She had passed through upper secondary school (gymnasium) and was at a secretarial school.

Case 52. E.K., born July 8, 1929. *XO/XX.* Fig. 16 *d.*

The patient had an apparently normal mental and physical development and had always been healthy.

She had consulted a gynaecological clinic repeatedly from the age of 18 years because of primary amenorrhea. An exploratory laparotomy at the age of 25 years revealed a very underdeveloped uterus and small, thin Fallopian tubes. From this finding the diagnosis of Turner's syndrome could be made. Only fibrous "streaks" were found at the sites of the ovaries. A histological examination was not made.

She was colour-blind. The mother and sister were said to have normal colour vision and the father was unknown to the patient.

The patient had passed through elementary school (folkskola) and had been working as an office girl for several years.

Case 53. S.Ö., born June 10, 1927. *XO/XX.*

The patient had always been of short stature but was healthy and had had an apparently normal mental development. She had a normal puberty with menarche between 15 and 16 years of age, but the menstruations were always irregular and sometimes with long intervals between.

The patient was referred to our clinic at 32 years of age because of the occurrence of secondary amenorrhea during the last half year, and the diagnosis of Turner's syndrome was made.

She had passed through elementary school (folkskola) and has been working as an office girl for many years. She was married at the age of 31 years, but the marriage was involuntarily sterile.

Case 54. E.H., born June 7, 1943. *XX.* Figs. 17 *b* and 18 *c.* Previously reported by *Almqvist et al.* (1963).

The patient was hospitalized at the age of 13 years because of acute meningo-encephalitis and she was operated upon at 17 years because of bilateral ptosis. She had always been of rather short stature but had a normal puberty with menarche at 11 years of age.

The patient had been physically weak, and because of difficulty in following the lessons had finished elementary school (folkskola) at the second last class. She had also been very nervous. The menstruations were regular to 17 years of age. Then amenorrhea began and she lost about 10 kg in weight, bringing her weight to about 26 kg. The breasts diminished in size and the nipples became paler, her nervousness increased and she sometimes became very depressed. She therefore consulted a physician at the age of 18 years and was referred to our clinic with the diagnosis of Turner's syndrome.

The investigations revealed that she also had Raynaud's disease, and it was likely that she had had a nervous anorexia. She also had a low urinary excretion of total gonadotrophins and oestrogens. A stimulation

test with gonadotrophins, however, gave a significant increase in the excretion of oestrogens.

The patient was incapable of having a job and was living with her parents, still very depressed.

Case 55. G.S., born October 29, 1939. $XO/XX_R/XX_RX_R$. Fig. 17 *c*. Previously reported by *Lindsten & Tillinger* (1962) and *Almqvist et al.* (1963).

The patient was hospitalized after birth because of neonatal melena. She had otherwise been healthy and had an apparently normal mental development. Her stature had always been short. She had a normal puberty and menarche at 12 years of age. The menstrual periods were regular and normal for about seven years, after which they became longer and once, at 19 years of age, it was thought that she had a spontaneous abortion. This could not be proved when a curettage was made.

Since then the patient has been hospitalized five times because of very irregular menstruations generally with long intervals. The diagnosis of Turner's syndrome was made at 20 years of age. She had never been submitted to any therapeutic X-ray irradiation. An exploratory laparotomy two years later showed a normal uterus and normal Fallopian tubes. The left ovary (2.8×3.1 cm) consisted almost exclusively of a thin-walled cyst. The right ovary (2.8×1.5 cm) was white, and the albuginea seemed to be thick. In one pole a small "cyst", a few millimeters in diameter, could be seen. No follicles were observed macroscopically. At histological investigation it was found that both gonads were ovaries. The number of primordial follicles was very low (Fig. 20 *g*). Their appearance seemed to be normal. The small "cyst" in the upper pole of the right ovary was a Graafian follicle. Only one more Graafian follicle was found. The cyst occupying the left ovary was a follicular cyst with only some remnants of granulosa cells but with a layer of distinct theca cells showing very scanty luteinisation (Fig. 20 *h*). Some atretic follicles could be seen, but no corpus albicans. The ovarian stroma was of the usual type. No diffuse stromal luteinisation of cells of Leydig type were found.

She had passed through elementary school (folkskola) and was working as a bookbinder's assistant.

Case 56. I.P., born July 27, 1938. XO/XX_D. Fig. 17 *d*.

The patient was hospitalized because of pneumonia at the age of three or four years and also because of several severe infections of the ears, the last time at seven years of age. Since then she had had bilateral hearing impairment. Every now and then, since the age of seven years, she had had albuminuria, probably orthostatic. She had always been of a very short stature but had an apparently normal mental development.

She was referred to our clinic at 12 years of age because of short stature, and the diagnosis of Turner's syndrome was made two years later.

The patient had finished elementary school (folkskola) and had been working as a cleaner for several years.

Case 57. E.B.H., born June 26, 1940. *XO/?*

The patient was hospitalized at six years of age because of converging strabismus and hyperopia and once more at the same age because of chronic tonsillitis. A tonsillectomy was performed. At the age of 12 years she was again hosiptalized because of severe infection of the left middle ear and a cholesteatoma. A radical operation was made. Two years later she was hospitalized again because of a severe infection of the ears. The patient had always been of short stature but had an apparently normal mental development.

She was referred to a gynaecological clinic at the age of 16 years with the diagnosis of Turner's syndrome. This diagnosis was based on the short stature, infantilism and very irregular menstruations. An exploratory laparotomy revealed a very underdeveloped uterus (1.5 cm long) and apparently normal but thin Fallopian tubes, while only fibrous "streaks" were found at the sites of the ovaries. Histological investigation showed an ovarian stroma-like structure without follicles and corpora lutea but with mesonephric ducts in the hilar region.

The patient and her father were colour-blind. The father was tested only with the Ishihara charts. The sibs and the mother have not been tested but were said to have normal colour vision.

The patient had finished elementary school (folkskola) and an adult continuation school (folkhögskola) and was working as a children's nurse.

TABLE 13. *Cytogenetical data and the incidence and type of colour-blindness.*

Patient		Chromosome analyses									Drumsticks per 500 neutrophil leucocytes	Sex chromatin in			Colour-blindness
			Distribution of chromosome counts						Total no. of cells counted	Sex chromosome constitution[b]		Skin sections	Cells from long-term cultures	Buccal mucosa smears,[c] per cent	
No.	Initials	Tissues[a]	⩽43	44	45	46	47	⩾48							
1	M. G.	B	3	7	90	—	—	—	100	XO	0	...	...	—	...
		S	—	—	18	—	—	—	18	XO			—		
2	S. B.	B	—	5	97	—	—	—	102	XO	0	...	...	—	...
		BM	—	—	14	—	—	—	14	XO			—		
		S	—	1	28	—	—	—	29	XO			—		
3	H. G.	B	4	4	96	—	—	—	104	XO	0	...	...	—	...
		S	2	1	49	—	—	—	52	XO			—		
4	M. L.	BM[d]	5	9	27	8	—	—	49	XO	0	...	—	...	—
		S	1	1	7	—	—	—	9	XO			—		
5	I. B. J.	B_1	6	1	47	—	—	—	54	XO	0	...	...	—	—
		B_2	2	1	27	—	—	—	30	XO			...		
		B_3	1	4	34	—	—	—	39	XO			...		
6	I. M. L.[e]	B	1	—	101	—	—	—	102	XO	0	...	...	—	—
		BM_S	—	—	41	—	—	—	41	XO			...		
7	M. B.	B	2	3	81	—	—	—	86	XO	0	...	...	—	—
8	I. B. H.	BM[d]	10	11	37	5	4	—	67	XO	...	—	—	...	...
9	V. G.[e]	B	3	2	55	—	—	—	60	XO	0	...	...	—	—
		BM[d]	—	3	29	1	—	—	33	XO			—		
10	L. J.	B_1	—	1	23	—	—	—	24	XO	0	...	...	—	—
		B_2	3	4	101	—	—	—	108	XO			...		
11	M. O.	B_1	—	1	39	—	—	—	40	XO	0	...	...	—	—
		B_2	1	2	58	—	—	—	61	XO			...		
		BM	—	—	6	—	—	—	6	XO			—		
		S	6	4	35	—	—	—	45	XO			—		
12	B. G.	B	2	1	49	—	—	—	52	XO	0	...	...	—	—
		S	5	1	20	—	—	—	26	XO			—		
13	K. A.	B_1	4	4	49	—	—	—	57	XO	0	—	...	—	—
		B_2	1	—	25	—	—	—	26	XO			...		
		B_3	3	2	47	—	—	—	52	XO			...		
14	L. L.	B_1	—	5	56	—	—	—	61	XO	0	...	...	—	—
		B_2	1	2	26	—	—	—	29	XO			...		
15	I. O.	B_1	—	1	24	—	—	—	25	XO	0	...	...	—	—
		B_2	5	3	70	—	—	—	78	XO			...		
16	C. L.	BM[d]	2	8	29	6	—	—	45	XO	...	—	—	...	...

Table 13 (*continued*)

Patient No.	Initials	Tissues[a]	Chromosome analyses: Distribution of chromosome counts ⩽43	44	45	46	47	⩾48	Total no. of cells counted	Sex chromosome constitution[b]	Drumsticks per 500 neutrophil leucocytes	Sex chromatin in: Skin sections	Cells from long-term cultures	Buccal mucosa smears,[c] per cent	Colour-blindness
17	B. H.	B	1	4	53	—	—	—	58	XO	0	...	...	—	—
		BM[d]	12	14	79	4	—	1	110	XO			—		
		S[d]	4	9	40	1	—	—	54	XO			—		
18	I. L.	B_1	—	2	24	—	—	—	26	XO	0	—	...	—	+
		B_2	—	2	25	—	—	—	27	XO			...		Deuter-anopia.
		B_3	2	4	49	—	—	—	55	XO			...		
19	K. S.	B	6	5	53	—	—	—	64	XO	0	...	...	—	—
		BM[d]	33	26	116	24	4	—	203	XO			—		
		S[d]	12	15	36	6	3	—	72	XO			—		
20	B. L.	B_1	1	2	33	—	—	—	36	XO	0	...	...	—	—
		B_2	—	—	51	—	—	—	51	XO			...		
21	D. F.	B_1	—	3	60	—	—	—	63	XO	0	...	...	—	—
		B_2	1	2	35	—	—	—	38	XO			...		
22	I. H.	B_1	1	—	43	—	—	—	44	XO	0	—	...	—	—
		B_2	1	2	53	—	—	—	56	XO			...		
		S	3	6	13	—	—	—	22	XO			—		
23	S. I. H.	B_1	—	1	60	—	—	—	61	XO	0	...	...	—	—
		B_2	—	—	52	—	—	—	52	XO			...		
24	I. A.	B_1	1	4	46	—	—	—	51	XO	0	...	...	—	—
		B_2	1	2	26	—	—	—	29	XO			...		
25	B. A.	B_1	2	3	49	—	—	—	54	XO	0	...	...	—	—
		B_2	2	1	24	—	—	—	27	XO			...		
		S	2	3	16	—	—	—	21	XO			—		
26	B. S-n.	B	—	3	69	—	—	—	72	XO	0	...	...	—	—
27	R. L.	B_1	—	2	36	—	—	—	38	XO	0	—	...	—	—
		B_2	—	7	60	—	—	—	67	XO			...		
28	V. S.	B	—	3	105	1[f]	—	—	109	XO	0	—	...	—	—
		BM	5	3	13	—	—	—	21	XO			—		
29	G. A.	B	—	3	77	—	—	—	80	XO	0	...	...	—	—
30	G. K.	B_1	—	1	51	—	—	—	52	XO	0	...	...	—	+
		B_2	2	3	46	—	—	—	51	XO			...		Deuter-anopia.
		S	1	—	7	—	—	—	8	XO			—		
31	A. F.[g]	B	4	7	98	—	—	—	109	XO	0	...	...	—	—
		S	4	4	24	—	—	—	32	XO			—		

Table 13 (*continued*)

Patient		Chromosome analyses									Sex chromatin in			
			Distribution of chromosome counts											
No.	Initials	Tissues[a]	⩽43	44	45	46	47	⩾48	Total no. of cells counted	Sex chromosome constitution[b]	Drumsticks per 500 neutrophil leucocytes	Skin sections	Cells from long-term cultures	Buccal mucosa smears,[c] per cent	Colour-blindness
32	M. N.	B_1	—	1	30	—	—	—	31	XO	0	...	...	—	—
		B_2	3	3	68	1[h]	—	—	75	XO			...		
33	M. S. L.	B_1	—	4	72	—	—	—	76	XO	0	—	...	—	—
		B_2	1	3	30	—	—	—	34	XO			...		
34	V. P.	B_1	—	4	25	—	—	—	29	XO	0	...	...	—	—
		B_2	—	1	21	—	—	—	22	XO			...		
		B_3	1	2	39	—	—	—	42	XO			...		
35	I. J.	B_1	3	7	56	—	—	—	66	XO	0	...	...	—	—
		B_2	—	2	50	—	—	—	52	XO			...		
36	Y. L.	B_1	—	—	—	48	—	—	48	XX_I	21	+	...	+	—
		B_2	—	2	—	38	—	—	40	XX_I			...	29	
		B_3	—	—	1	49	—	—	50	XX_I			...		
		S_H	3	9	6	86	—	—	104	XX_I			+		
37	G. E.	B_1	—	3	25	36	—	—	64	XO/XX_I	8	+	...	+	—
		B_2	2	3	15	29	—	—	49	XO/XX_I			...	23	
38	B. J.	B	—	3	26	71	—	—	100	XO/XX_I	12	+	...	+	+
		S	—	7	3	38	—	—	48	XO/XX_I			+	32	Probable deuteranopia.
		S_H	—	7	31	28	—	—	66	XO/XX_I			+		
39	B. S.	B_1	1	1	33	28	—	—	63	XO/XX_I	9	...	...	+	—
		B_2	2	3	30	16	—	—	51	XO/XX_I			...	11	
40	A. S.[f]	B_1	—	1	13	32	—	—	46	XO/XX_I	25	+	...	+	—
		B_2	—	4	33	24	—	—	61	XO/XX_I			...	21	
		BM_1[e]	—	6	8	38	4	—	56	XO/XX_I			+		
		BM_2	—	—	1	18	—	—	19	XO/XX_I			+		
		S[e]	—	1	2	25	3	—	31	XO/XX_I			+		
41	L. A.[f]	B	1	5	41	54	—	—	101	XO/XX_I	10	+	...	+	—
		BM	—	5	1	27	—	—	33	XO/XX_I			+	34	
		S_H	—	5	27	59	—	—	91	XO/XX_I			+		
42	C. S.	B_1	1	4	47	—	—	—	52	XO	2	+	...	+	—
		B_2	—	2	53	2	—	—	57	XO/XX_I			...	14	
		S_H	6	7	63	6	—	—	82	XO/XX_I			+		
43	E. S.	B_1	1	4	19	33	8	—	65	$XO/XX_I/XX_I X_I$	9	...	...	+ 27	—
		B_2	4	2	30	39	4	—	79	$XO/XX_I/XX_I X_I$			...		

Table 13 (*continued*)

Patient No.	Patient Initials	Tissues[a]	Chromosome analyses: Distribution of chromosome counts ⩽43	44	45	46	47	⩾48	Total no. of cells counted	Sex chromosome constitution[b]	Drumsticks per 500 neutrophil leucocytes	Sex chromatin in: Skin sections	Cells from long-term cultures	Buccal mucosa smears,[c] per cent	Colour-blindness
44	M. A.[e, i]	B_1	—	3	1	41	—	—	45	XX_I	22	+	...	+	-
		B_2	—	—	—	47	—	—	47	XX_I			...	36	
		B_3	—	3	9	72	—	—	84	XX_I			...		
		BM_1[j]	—	7	6	36	3	—	52	XX_I			+		
		BM_2[j]	—	2	2	9	3	—	16	XX_I			+		
		BM_3	—	—	—	13	—	—	13	XX_I			+		
		S_H	—	—	1	102	—	—	103	XX_I			+		
45	M. J.	B	—	—	9	40	—	—	49	XO/XX_I	...	...	...	+ 26	—
46	R. K.	B_1	2	2	55	18	—	—	77	XO/XX_I	6	...	...	+	—
		B_2	—	2	34	18	—	—	54	XO/XX_I			...	27	
47	M. C.	B_1	—	4	62	—	—	—	66	XO	0	...	...	+	—
		B_2	—	—	56	—	—	—	56	XO			...	7	
		S_H	4	3	32	13	—	—	52	XO/XX			+		
		O	—	1	17	7	—	—	25	XO/XX			+		
48	S. S.	BM[j]	—	10	31	51	5	—	97	XO/XX	...	...	+	...	—
		S[j]	—	3	36	2	1	—	42	XO/XX			+		
49	B. N.	B_1	—	2	11	98	—	—	111	XO/XX	10	...	...	+	—
		B_2	—	—	9	27	—	—	36	XO/XX			...	31	
50	A. H.	B_1	—	2	40	9	—	—	51	XO/XX	8	+	...	+	—
		B_2	—	3	20	8	—	—	31	XO/XX			...	16	
		S_H	—	1	35	15	—	—	51	XO/XX			+		
51	M. H.	B_1	1	—	50	2	—	—	53	XO	0	...	...	+	—
		B_2	2	—	31	—	—	—	33	XO			...	21	
		S_H	1	1	25	25	—	—	52	XO/XX			+		
52	E. K.	B_1	—	2	41	10	—	—	53	XO/XX	3	...	...	+	+ Extreme deuter-anomaly.
		B_2	—	2	43	7	—	—	52	XO/XX			...	9	
53	S. Ö.	B_1	3	6	56	36	—	—	101	XO/XX	5	...	...	+	—
		B_2	—	1	38	15	—	—	54	XO/XX			...	20	
54	E. H.	B	—	1	2	97	—	—	100	XX	9	...	...	+	—
		S_H	2	5	8	96	—	—	111	XX			+	22	
55	G. S.[k]	B_1	—	3	22	11	—	—	36	XO/XX_R	9	...	...	—	—
		B_2	1	3	78	38	2	—	122	$XO/XX_R/XX_R X_R$			...		

Table 13 (*continued*)

Patient No.	Patient Initials	Tissues[a]	Chromosome analyses: Distribution of chromosome counts ⩽43	44	45	46	47	⩾48	Total no. of cells counted	Sex chromosome constitution[b]	Drumsticks per 500 neutrophil leucocytes	Sex chromatin in: Skin sections	Cells from long-term cultures	Buccal mucosa smears,[c] per cent	Colour-blindness
55	G. S.[k]	B_3	—	—	21	13	1	—	35	$XO/XX_R/XX_R X_R$			···		
		B_4	—	1	37	11	2	—	51	$XO/XX_R/XX_R X_R$			···		
		B_5	2	4	58	20	—	—	84	XO/XX_R			···		
		B_6	—	—	31	16	1	—	48	$XO/XX_R/XX_R X_R$			···		
		B_7	6	4	88	33	1	—	132	$XO/XX_R/XX_R X_R$			···		
		S_{1H}	6	6	143	—	—	—	155	XO			—		
		S_{2Ha}	1	3	27	4	—	—	35	XO/XX_R			+		
		S_{2Hb}	2	7	32	—	1[l]	—	42	XO			—		
		BM_{Ha}	—	—	23	6	—	—	29	XO/XX_R			+		
		BM_{Hb}	—	5	25	—	—	—	30	XO			—		
		L_a	3	7	59	10	2[l]	—	81	XO/XX_R			+		
		L_b	4	1	44	1	—	—	50	XO/XX_R			—		
		O_H	—	—	37	—	—	—	37	XO			—		
56	I. P.	B_1	—	2	60	17	—	—	79	XO/XX_D	9	+	···	+	
		B_2	2	3	35	9	—	—	49	XO/XX_D			···	18	
		S_H	2	2	46	49	—	—	99	XO/XX_D			+		
57	E. B. H.	B_1	—	2	12	—	—	—	14	XO	0	—	···	+	+
		B_2	5	4	46	—	—	—	55	XO			···	10	Extreme deuter-anomaly.
		S_H	—	—	100	—	—	—	100	XO			—		

[a] B = cultures of peripheral blood.
BM_S = short-term incubation of a bone marrow biopsy.
BM = long-term cultures of cells from bone marrow biopsies according to *Fraccaro et al.* (1960 *c*).
BM_H = long-term cultures of cells from a bone marrow biopsy according to *Hsu & Kellogg* (1960).
S = long-term cultures of cells from skin biopsies according to *Fraccaro et al.* (1960 *c*).
S_H = long-term cultures of cells from skin biopsies according to *Hsu & Kellogg* (1960).
L = long-term cultures of cells from a lymph node according to *Hsu & Kellogg* (1960).
O = long-term cultures of cells from ovarian biopsies according to *Hsu & Kellogg* (1960).
When several specimens from the same tissue were studied in a case, they have been numbered in chronological order.
Special notes for Case 55.
S_{2Ha} = two weeks with two transplantations *in vitro*.
S_{2Hb} = one month with one transplantation *in vitro*.
BM_{Ha} = one week *in vitro* without transplantation.
BM_{Hb} = one month with one transplantation *in vitro*.
L_a = two weeks with one transplantation *in vitro*.
L_b = one month with four transplantations *in vitro*.

[b] X_I = presumptive iso-chromosome for the long arm of the X chromosome.
X_R = ring chromosome of the X chromosome.
X_D = probable deletion of the short arm of the X chromosome.

[c] Normal variation in this laboratory was 31 ± 3 per cent in 20 apparently normal adult females. Only sex chromatin bodies at the nuclear membrane were counted.

[d] The cells with 46 chromosomes showed no constant karyotype. They are thought to have resulted almost exclusively from technical errors, as squash preparations were used.

[e] Both parents had apparently normal karyotypes in leucocytes from cultures of peripheral blood.

[f] This cell had an extra chromosome similar to those of the group 13–15.

[g] A twin brother had an apparently normal male karyotype in leucocytes from cultures of peripheral blood.

[h] This cell had an extra chromosome in the group 6–12.

[i] A twin sister had an apparently normal female karyotype in leucocytes from cultures of peripheral blood.

[j] The cells with 47 chromosomes showed no constant karyotypes. They are thought to have resulted almost exclusively from technical errors, as squash preparations were used.

[k] The father had an apparently normal male sex chromosome constitution in leucocytes from cultures of peripheral blood. The mother was dead.

[l] These cells had one extra chromosome in the group 6–12 but no ring chromosome.

TABLE 14. *Family data.*

No.	Patient: Initials	Patient: Sex chromosome constitution	Parental ages at the birth of the patient: Mother	Parental ages at the birth of the patient: Father	Position in sibship[a]	Sibs[b]: Brothers	Sibs[b]: Sisters	Spontaneous abortions of the mother	Parents' sibs[b]: Mother's: Brothers	Parents' sibs[b]: Mother's: Sisters	Parents' sibs[b]: Father's: Brothers	Parents' sibs[b]: Father's: Sisters	First cousins[b]: Mother's side: Males	First cousins[b]: Mother's side: Females	First cousins[b]: Father's side: Males	First cousins[b]: Father's side: Females	Twins[c]
1	M. G.	XO	34	49	1/1	—	—	—	1	—	2	3	—	1	2	5	—
2	S. B.	XO	35	32	2/2	—	1	—	1	1	2	—	3	2	—	4	—
3	H. G.	XO	27	27	2/2	1	—	—	—	—	2	1	—	—	6	3	—
4	M. L.	XO	39	40	1/1	—	—	...	...	...	...	...	...	...	...	...	—
5	I. B. J.	XO	32	39	2/4	2	1	—	1	2	2	1	2	7	6	1	—
6	I. M. L.	XO	37	42	4/4	1	2	—	4	2	6	2	2	2	9	9	Mother's sibs, FF.
7	M. B.	XO	34	32	2/3	1(1)[1]	—	6	—	2	3	3	4	2	5[1]	3	—
8	I. B. H.	XO	29	30	1/4	1	2	1	...	...	...	...	...	...	...	...	...
9	V. G.	XO	21	23	1/4	3	—	—	1	1	—	(1)	—	1	—	—	—
10	L. J.	XO	32	37	1/1	—	—	—	2	2	—	—	1	2	—	—	—
11	M. O.	XO	34	35	7/10	3	6	2	5	5	6	4	19	15	7	17	Father's sibs, FF. Paternal first cousins, FF.
12	B. G.	XO	33	34	1/2	—	1	—	2	1	—	1	—	3	1	1	—
13	K. A.	XO	25	30	1/2	—	1	—	—	—	1	4	—	—	4	2	—
14	L. L.	XO	20	...	1/2	(1)	—	—	1	1	...	...	1	2	...	...	—
15	I. O.	XO	37	40	2/2	1	—	1	—	1	4	2	2	1	10	5	—
16	C. L.	XO	33	36	2/2	1	—	1	—	2	3	2	...	...	...	...	...
17	B. H.	XO	32	35	2/3	2	—	1	1	2	6	3	9	4	10	7	Father's sibs, MM. Maternal first cousins, MF.
18	I. L.	XO	24	25	1/5	3	2	—	3	2	—	4	4	9	—	2	Sibs, MF. Father's sibs, FF.
19	K. S.	XO	20	19	1/5	1(2)	(1)	—	4	6	...	...	6[2]	5(1)	...	...	—
20	B. L.	XO	36	38	3/3	2	—	—	2	3	2	2	2	1	1	3	The father, MF.
21	D. F.	XO	25	26	2/3	1	1	3	1	1	1	1	1	3	2	2	—
22	I. H.	XO	28	43	2/2	—	1	—	2	—	3	1	1	—	3	3	Mother's sibs, MM.
23	S. I. H.	XO	18	24	1/3	—	2	—	—	—	1	3	—	—	4	4	The maternal grandmother, FF.
24	I. A.	XO	29	32	1/2	—	1	—	3	2	2	3	4	4	3	8	—
25	B. A.	XO	26	27	1/3	1	1	—	2	3	—	5	6	2	4	5	—
26	B. S-n.	XO	32	43	1/1	—	—	1	1	2	...	...	1	4	...	...	—
27	R. L.	XO	28	39	1/3	(2)	—	—	1	—	1	—	[2]	—	—	—	—
28	V. S.	XO	19	21	1/2	1	—	—	1(1)	4(1)	—	1	6(1)	1	2	—	Mother's sibs, MF.
29	G. A.	XO	22	35	1/1	—	—	—	—	—	2	1	—	—	1[1]	2(2)	—
30	G. K.	XO	23	29	1/3	1	1	—	—	2	1	2	—	1	3	6	Paternal first cousins MF. Paternal grandfather, MM.
31	A. F.	XO	29	37	2/2	2	—	—	5	2	3	3	8	7	5	2	The patient, MF.
32	M. N.	XO	38	38	2/2	1	—	—	4	6	2	4	11	13	3	6	Maternal first cousins FF, MF.

Table 14 (*continued*)

Patient			Parental ages at the birth of the patient		Position in sibship[a]	Sibs[b]		Spontaneous abortions of the mother	Parents' sibs[b]				First cousins[b]				Twins[c]
									Mother's		Father's		Mother's side		Father's side		
No.	Initials	Sex chromosome constitution	Mother	Father		Brothers	Sisters		Brothers	Sisters	Brothers	Sisters	Males	Females	Males	Females	
33	M.S.L.	XO	36	36	4/4	2	1	1	2	2	2	4	3	3	—	1	—
34	V.P.	XO	22	26	2/3	2	—	1	3	2	2	2	3	5	1	1	Maternal first cousins FF.
35	I.J.	XO	30	33	3/4	3	—	—	1	1	2	4	2	3	12	9	—
36	Y.L.	XX_I	23	30	2/4	3	—	—	4	1	6	1	9	8	9	10	Mother's sibs, MM.
37	G.E.	XO/XX_I	21	30	2/2	—	1	—	2	2	—	2	6	7	4	1	The paternal grandfather, MM. Paternal first cousins, FF.
38	B.J.	XO/XX_I	25	33	2/6	5	1	1	2	—	2	2	1	—	2	6	Sibs, MM. Paternal first cousins, FF.
39	B.S.	XO/XX_I	26	27	1/3	1	1	—	1	5	—	1	1	4	1	—	—
40	A.S.	XO/XX_I	28	30	2/2	—	1	—	2	3	4	4	10	5	6	7	Maternal first cousins MM.
41	L.A.	XO/XX_I	35	51	3/3	2	—	1	2	2	3	4	2	1	3	2	The father, MF.
42	C.S.	XO/XX_I	33	43	4/5	2	2	3	—	2	1	1	7	1	1	3	Maternal first cousins MF.
43	E.S.	$XO/XX_I/XX_I\,X_I$	22	27	1/1	—	—	–	1	—	…	…	—	—	…	…	—
44	M.A.	XX_I	35	31	2/2	1	1	—	(1)	—	2	1	1	2	2	2	The patient, FF.
45	M.J.	XO/XX_I	36	37	4/4	—	3	1	1	1	5	3	1	3	4	2	—
46	R.K.	XO/XX_I	24	32	4/4	3	—	1	1	—	2	3	3	—	9	2	—
47	M.C.	XO/XX	30	28	1/2	—	1	1	—	1	(1)	—	—	—	—	—	—
48	S.S.	XO/XX	29	28	1/2	1	—	…	…	…	…	…	…	…	…	…	…
49	B.N.	XO/XX	31	32	3/4	1(1)	1	—	2	1	—	1[2]	3	1	1(3)	1	—
50	A.H.	XO/XX	28	43	2/3	2	—	—	2	1[2]	1	6	1[6]	1[1]	5	4	Maternal first cousins MF. Paternal first cousins, MM.
51	M.H.	XO/XX	32	34	2/3	1	1	—	1	1	—	—	3	3	—	—	·
52	E.K.	XO/XX	22	…	1/2	—	(1)	—	4	3	…	…	8	7	…	…	—
53	S.Ö.	XO/XX	35	32	5/7	3	3	—	1	2	—	—	2	3	—	—	—
54	E.H.	XX	34	39	2/2	—	1	1	—	—	2	2	—	—	7	1	—
55	G.S.	$XO/XX_R/XX_R\,X_R$	29	30	1/1	[1]	—	1	2	1	2	3	3	1	3	1	—
56	I.P.	XO/XX_D	42	45	3/3	2	—	—	1	5	2	1	10	4	5	3	—
57	E.B.H.	XO/?	22	29	3/5	1	2(1)	—	5	1	5	2	3	3	4	6	Paternal first cousins FF.

[a] Maternal but not paternal half-sibs were included in this calculation.
[b] Sibs within brackets were maternal half-sibs and those within square brackets were paternal half-sibs.
[c] F = female; M = male.

TABLE 15. *Laboratory data.*

Patient			Serum[a]											Radio-iodine test,[b] per cent				
No.	Initials	Sex chromosome constitution	Sodium, mE/l	Potassium, mE/l	Chloride, mE/l	Bicarbonate, mE/l	Calcium, mE/l	Inorganic phosphate, mmol/l	Alkaline phosphatase, U/100 ml	Acid phosphatase, U/100 ml	Cholesterol, mg/100 ml	Protein-bound iodine, µg/100 ml	Total serum protein and electrophoresis	T 24	U 24	Basal metabolic rate, per cent	Intravenous glucose tolerance test,[c] *k*-value	Miscellaneous tests
1	M. G.	XO	...	...	...	...	...	...	...	...	...	...	—[d]	...	...	...	...	
2	S. B.	XO	134	...	107	21	...	...	...	...	...	...		...	...	...	...	Normal electroencephalogram.
3	H. G.	XO	138	4.6	...	...	...	...	9–13	...	...	...	[e]	...	...	...	...	Normal amino acid pattern in urine.
4	M. L.	XO	...	...	...	...	5.7	0.58	...	...	...	...	...	...	...	...	...	
5	I. B. J.	XO	135	4.5	98	25	4.9	0.47	10–15	1	195	6.6		42	48	−2	1.93	
6	I. M. L.	XO	140	4.3	101	23	5.1	0.37 0.41	9	1	185	5.8	—	43	40	+6	2.07	
7	M. B.	XO	138	3.9	102	21	4.8	0.46	6	...	233	5.8 6.1	—	...	...	−17	...	Normal electroencephalogram.
8	I. B. H.	XO	...	...	...	...	...	...	...	...	170	...	...	...	...	−3 +6	...	
9	V. G.	XO	138	4.1	100	28	5.2	0.43	5	1	185	5.0	—	49	37	−3	...	Normal amino acid pattern in urine.
10	L. J.	XO	133	4.3	103	25	5.1	0.45	8	...	215	6.8	...	35	26	−1	...	
11	M. O.	XO	135	3.9	101	24	5.2	0.41	5	...	333 288	6.3	—	23	55	−2	1.35 0.75	
12	B. G.	XO	140	3.9	109	...	5.2	0.41	10	1	271	4.8	—	...	...	−5	1.41	Normal ACTH test and water load test.
13	K. A.	XO	137	4.2	104	26	5.0	0.35	6	...	270 253	8.2	...	48	46	+6 −11	—	
14	L. L.	XO	142	4.5	100	28	5.1	0.56	4	1	342	6.4	—	...	...	...	...	

15	I. O.	XO	139	3.9	100	23	5.0	0.45	3	0	200	5.1	—	...	...	+ 1	2.52	
16	C. L.	XO	138	4.2	...	...	...	0.38	9	...	...	7.2	...	...	...	− 2	...	
17	B. H.	XO	135	4.4	97	28	4.7	0.41	7	0	236	6.8	—	...	...	+ 3	...	
											170							
18	I. L.	XO	137	4.5	99	25	5.2	0.38	6	0	284	7.7	—	47	26	+ 14	...	
19	K. S.	XO	...	...	...	...	...	...	...	...	254	5.7	...	...	...	...	...	
20	B. L.	XO	138	4.1	99	29	4.9	0.37	2	1	208	11.1	—	...	...	± 0	2.43	Normal water load test.
											249					+ 11		
21	D. F.	XO	143	4.2	107	23	5.1	0.40	4	0	239	7.4	—	...	...	− 15	...	Normal water load test.
22	I. H.	XO	140	4.3	100	24	4.7	0.36	3	0	210	6.0	—	...	...	...	2.07	Normal water load test.
23	S. I. H.	XO	138	3.9	101	29	6.0	0.43	3	1	163	5.6	-	...	...	...	3.64	
											190							
24	I. A.	XO	140	3.6	102	23	5.1	0.32	7	1	303	6.9	—	...	...	− 7	1.82	Normal insulin tolerance and water load tests.
											220							
25	B. A.	XO	140	3.9	99	24	1.2	0.45	6	1	290	6.3	—	...	...	+ 1	...	Normal ACTH test.
26	B. S-n.	XO	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	
27	R. L.	XO	142	4.3	99	29	7.0	0.41	...	1	223	6.0	—	...	...	- 7	...	
								0.44										
28	V. S.	XO	...	...	104	27	...	0.47	5	...	248	4.2	—	...	...	− 4	1.12	
29	G. A.	XO	140	4.5	105	27	4.9	0.39	5	1	185	8.3	...	...	...	+ 2	...	
30	G. K.	XO	140	4.5	98	28	4.9	0.28	5	1	256	4.2	—	...	...	− 11	...	Normal insulin tolerance and water load tests.
											251							
31	A. F.	XO	138	4.0	97	25	5.1	0.29	3	1	268	6.4	...	...	...	+ 15	2.01	Normal insulin tolerance and water load tests.
								0.35										
32	M. N.	XO	139	4.2	105	25	5.1	0.35	5	1	289	5.9	—	...	...	- 1	1.86	Normal water load test and normal electroencephalogram.
											304							
33	M. S. L.	XO	139	6.5	107	27	5.0	0.31	6	1	213	8.3	—	...	...	− 3	...	Normal insulin tolerance test.
											156					− 7		

Table 15 (*continued*)

Patient			Serum[a]											Radio-iodine test,[b] per cent				
No.	Initials	Sex chromosome constitution	Sodium, mE/l	Potassium, mE/l	Chloride, mE/l	Bicarbonate, mE/l	Calcium, mE/l	Inorganic phosphate, mmol/l	Alkaline phosphatase, U/100 ml	Acid phosphatase, U/100 ml	Cholesterol, mg/100 ml	Protein-bound iodine, µg/100 ml	Total serum protein and electrophoresis	T 24	U 24	Basal metabolic rate, per cent	Intravenous glucose tolerance test,[c] *k*-value	Miscellaneous tests
34	V. P.	XO	137	4.3	104	26	4.9	0.42	4	0	242	7.5	—	…	…	…	…	
35	I. J.	XO	141	4.3	104	…	5.0	0.34	4	…	230 299	4.4	…	…	…	− 18	1.78	
36	Y. L.	XX_I	134	4.2	99	19	5.2	0.50 0.53	11	1	248	7.3	—	…	…	+ 5	1.83	
37	G. E.	XO/ XX_I	140	4.1	104	24	5.1	0.34 0.45	3 5	0	244 266	7.3 7.8	—	…	…	− 5	…	
38	B. J.	XO/ XX_I	137	4.3	104	26	5.0	0.36 0.42	3 5	0	239 228	4.7	—	34	47	− 1	2.17	Normal amino acid pattern in urine and water load test.
39	B. S.	XO/ XX_I	142	4.7	104	25	5.0	0.45	6	1	323 287	6.8	—	…	…	− 3	…	Normal endogenous creatinine, inulin and PAH clearances, normal amino acid pattern in urine.
40	A. S.	XO/ XX_I	140	3.8	101	27	5.4	0.42	3	1	238	7.4	—	…	…	+ 1	1.71	Normal amino acid pattern in urine.
41	L. A.	XO/ XX_I	143	4.3	107	25	5.0	0.42	6	…	296	7.5	—	50	39	…	1.73	Normal water load test.
42	C. S.	XO/ XX_I	134	4.4	106	22	4.6	0.39	5	1	234 253	5.5	—	…	…	− 3 + 18	2.13	Normal ACTH test, general dysrythmia on electroencephalogram.

43	E. S.	$XO/XX_I/XX_IX_I$	...	...	...	...	...	0.43	6	0	234	...	—	...	...	+9	...	
44	M. A.	XX_I	138	3.8	102	21	4.9	0.27	4	1	200	10.7	...	37	40	+27 +32	...	
45	M. J.	XO/XX_I	...	...	...	...	...	0.41	...	...	177 258	6.1	...	...	...	+11	...	Normal insulin tolerance test.
46	R. K.	XO/XX_I	144	4.2	100	25	4.8	0.37	6	1	216 200	6.0	—	...	...	+7 −18	...	Normal insulin tolerance and water load tests.
47	M. C.	XO/XX	...	...	...	...	...	...	...	...	290 330	6.0	...	...	...	−2 −4	...	See Case report with regard to electroencephalogram.
48	S. S.	XO/XX	...	...	...	...	...	...	...	...	...	...	...	...	...	+3	...	
49	B. N.	XO/XX	139	4.2	100	28	5.0	0.48	11	1	211	5.3	—	...	...	−12	...	
50	A. H.	XO/XX	135	4.2	105	25	5.0	0.51	5	...	275	5.8	—	...	...	±0	...	Normal oral glucose tolerance test.
51	M. H.	XO/XX	...	...	...	24	4.9	0.41	3	1	176 258	6.8	—	...	...	−6	...	
52	E. K.	XO/XX	145	4.4	98	28	4.9	...	3	1	303	5.3	—	...	...	−6	...	Normal oral glucose tolerance test.
53	S. Ö.	XO/XX	141	4.9	99	...	5.1	0.32	3	1	243	8.2	...	...	...	+5	...	
54	E. H.	XX	140	4.2	99	29	5.3	0.41	3	0	285	6.0	—	38	48	−26	2.31	
55	G. S.	$XO/XX_R/XX_RX_R$	139	4.3	104	27	4.9	0.39	4	...	227	7.3	—	...	...	−20	2.00	
56	I. P.	XO/XX_D	138	5.4	103	26	5.1	0.51	4	1	285 294	6.4	—	...	...	+2 +3	—	Normal insulin tolerance and water load tests.
57	E. B. H.	XO/?	...	...	...	...	5.1	0.42	4	...	278	...	...	...	...	...	...	

[a] In this laboratory normal values for adult individuals were:
sodium 135–145 mE/l
potassium 4.0–6.0 mE/l
chloride 95–110 mE/l
bicarbonate 25–35 mE/l
calcium 4.7–5.4 mE/l
inorganic phosphate 0.42–0.74 mmol/l
alkaline phosphatase 2–10 U/100 ml
acid phosphatase $\leqslant 2$ U/100 ml
cholesterol 150–300 mg/100 ml
protein-bound iodine 4–8 μg/100 ml
− = normal electrophoretic pattern and normal amount of total serum protein, i.e. 6.5–8.0 g/100 ml for adults and 5.3–8.8 g/100 ml for children below one year of age.

[b] $T_{24} = {}^{131}I$ uptake by the thyroid gland after 24 hours.
$U_{24} = {}^{131}I$ excretion in the urine during the first 24 hours.
In this laboratory all values were considered to be normal except in Cases 10 and 18 where T_{24} was within normal limits but U_{24} was somewhat low.

[c] $k < 0.95$ indicates decreased glucose tolerance.

[d] The patient had one decreased and one normal value for total serum protein.

[e] The patient had two decreased values for total serum protein.

TABLE 16. *Hormone analyses.*

Patient			Oestrogens in urine (before treatment)				Urinary total gonadotrophins, mg HMG-20 A/24 h[c]		17-ketosteroids in urine,[d] mg/24 h, range	17 ketogenic steroids in urine,[d] mg/24 h, range	Sulphation factor activity in serum,[e] U/ml
				Chemical determination,[b] μg/24h							
No.	Initials	Sex chromosome constitution	Biological determination,[a] MU/24 h	Oestrone	17 β-oestradiol	Oestriol	Before oestrogen therapy	During oestrogen therapy			
1	M. G.	XO	...	...	...	...	< 3	...	0.3	1.2	1.05
2	S. B.	XO	...	...	...	...	~ 6				
							~ 6	...	...	...	0.69
3	H. G.	XO	< 10	...	...	...	> 24				
							< 3	...	0.7	0.6	0.90
4	M. L.	XO	< 10	...	...	...	~ 12[f]				
							~ 16	...	...	...	...
5	I. B. J.	XO	< 10	0.9	0	0.4	> 45	...	2.6– 9.1	6.0–11.6	...
6	I. M. L.	XO	< 10	1.4	1.5	0	~ 45	...	2.0– 4.3	6.1– 9.7	1.34
7	M. B.	XO	< 10	...	...	...	> 24				
							> 90	...	5.0– 8.6	5.6– 8.0	1.25
8	I. B. H.	XO	< 20	...	...	...	> 45 < 90	...	4.8– 7.3	10.8–13.9	...
9	V. G.	XO	< 20	...	...	...	> 45	< 6	5.2– 7.2	13.3–13.9	0.68
10	L. J.	XO	< 20	...	...	...	> 45	> 3 < 6	2.5– 4.8	6.8–13.6	1.81
11	M. O.	XO	~ 10	1.8	1.5	1.0	> 24 < 45	> 6 < 24	3.8– 9.5	2.6–14.9	1.45
12	B. G.	XO	< 10	...	...	...	> 45	...	2.7– 3.6	6.7–10.8	...
13	K. A.	XO	< 10	...	...	...	~ 45	< 6	2.1– 4.2	1.1– 8.0	1.13
14	L. L.	XO	< 10	...	...	...	> 45 < 90	...	2.1– 4.2	1.1– 8.0	1.13
15	I. O.	XO	< 10	...	...	...	~ 24	~ 6	1.0– 4.8	4.5–12.4	0.90
16	C. L.	XO	< 20	4.3	3.5	0.4	~ 90	...	5.8	18.7	...
17	B. H.	XO	< 20	...	...	...	> 45	> 3 < 6	5.4– 6.9	7.4– 8.1	...
18	I. L.	XO	< 20	2.5	2.2	0	> 45	> 6 < 24	6.0– 7.0	9.5–11.3	1.40
19	K. S.	XO	~ 20	...	...	...	> 90	...	4.4	14.8	...
20	B. L.	XO	...	...	...	...	...	> 24 < 45	2.6– 7.2	2.4– 9.9	...
21	D. F.	XO	< 10	...	...	...	> 90				
							~ 24	...	5.7– 8.6	8.5–12.5	...
22	I. H.	XO	< 20	...	...	...	> 6 < 24	< 6	3.2– 6.0	6.1– 9.3	0.82
23	S. I. H.	XO	< 10	...	...	...	> 45 < 90	...	2.4– 6.4	7.6–12.5	...
							> 45				
24	I. A.	XO	< 10	...	...	...	> 45	...	4.4– 5.0	7.9–13.8	...
							> 45 < 90				
25	B. A.	XO	~ 50	...	...	...	> 45				
							< 3	...	3.5– 4.8	9.1–11.8	...
26	B. S-n.	XO	< 10	...	...	...	< 6	...	2.4	5.3	...
27	R. L.	XO	< 20	...	...	...	> 45	< 6	4.2– 6.2	3.8– 9.9	...
28	V. S.	XO	< 20	2.0	0	0	> 45	...	7.1– 7.8	3.0–11.0	2.27
							> 6 < 24				
29	G. A.	XO	20	...	...	...	~ 45	...	2.8– 3.0	7.0– 7.4	...
30	G. K.	XO	...	...	...	...	> 45	< 3	3.0– 4.6	2.3– 5.0	0.83
31	A. F.	XO	< 10	...	...	...	> 90	...	5.7– 6.7	10.6–15.3	21.8
							> 24 < 45				
32	M. N.	XO	< 10	...	...	...	~ 24	< 6	2.8– 3.0	7.0– 7.4	1.29
							> 24 < 45				

[a] One mouse unit (MU) was equivalent to the biological activity of about 0.1 μg oestrone. All determinations gave decreased values except in Cases 25 and 55 where normal values were obtained. Cases 43 could not be evaluated further.

[b] All cases had decreased levels except Cases 48, 55 and 57 in whom the determinations gave normal or low values.

Table 16 (*continued*)

Patient			Oestrogens in urine (before treatment)					Urinary total gonadotrophins, mg HMG-20 A/24 h[c]		17-ketosteroids in urine,[d] mg/24 h, range	17 ketogenic steroids in urine,[d] mg/24 h, range	Sulphation factor activity in serum,[e] U/ml
				Chemical determination,[b] μg/24h								
No.	Initials	Sex chromosome constitution	Biological determination,[a] MU/24 h	Oestrone	17 β-oestradiol	Oestriol		Before oestrogen therapy	During oestrogen therapy			
33	M. S. L.	XO	...	...	...	...		> 24 < 45	...	2.8– 4.5	10.5	...
34	V. P.	XO	< 110	...	...	...		> 24 < 45	...	2.3– 2.9	9.2–12.3	...
			< 20					> 6 < 24				
								> 45				
35	I. J.	XO	< 10	3.3	1.6	3.2		~ 24	...	5.5– 9.4	10.6	2.03
36	Y. L.	XX_I	< 10	0.5	0.1	0.7		< 3				
								< 3	...	2.5– 3.8	5.8– 7.9	1.88
37	G. E.	XO/XX_I	< 10	2.2	0	0		> 24 < 45	> 3 < 6	3.4– 6.2	5.9– 8.2	0.59
38	B. J.	XO/XX_I	< 10	...	...	...		> 24	< 6	2.5– 5.3	7.0–12.1	1.17
39	B. S.	XO/XX_I	< 20	...	...	...		> 45	> 6 < 12	4.7– 4.9	7.3– 9.4	1.53
40	A. S.	XO/XX_I	< 10	...	...	...		> 45	< 3	3.4– 4.8	3.9– 8.6	2.16
41	L. A.	XO/XX_I	< 20	0.9	3.4	0.2		> 6 < 45	...	3.7– 9.6	6.7–18.5	1.57
								> 45				
42	C. S.	XO/XX_I	< 10	...	...	...		> 45	> 6 < 24	3.9– 8.3	8.3– 9.6	...
43	E. S.	$XO/XX_I/XX_IX_I$	< 50	4.1	1.7	2.8		> 24 < 45	...	3.8	...	...
								> 12 < 24				
								> 45 < 90				
44	M. A.	XX_I	< 10	...	...	...		> 45 < 135	...	5.4– 6.6	10.2–11.6	0.86
								> 90				
45	M. J.	XO/XX_I	~ 10	...	...	...		> 90	...	7.8– 8.5	10.5–13.0	...
								> 45 < 90				
46	R. K.	XO/XX_I	< 10	...	...	...		> 135	~ 6	3.2– 4.5	6.8– 7.8	...
								> 45 < 90				
47	M. C.	XO/XX	< 10	...	...	...		> 45 < 90	...	11.9	17.0	1.15
								> 12				
48	S. S.	XO/XX	< 10	5.5	2.4	12.5		> 45	...	4.2– 8.6	9.6–10.7	...
				3.5	0.4	5.9		> 36				
49	B. N.	XO/XX	< 10	...	...	...		> 45 < 192	> 3 < 6	6.3– 8.9	8.7–12.0	...
50	A. H.	XO/XX	< 10	2.5	0	0		~ 45				
								> 45	...	6.4–12.8	9.6–17.2	1.02
51	M. H.	XO/XX	...	...	...	...		...	> 6 < 12	5.0– 8.4	6.9–12.9	...
52	E. K.	XO/XX	< 10	...	...	...		> 24 < 45	< 6	4.5– 6.0	6.5–10.8	...
53	S. Ö.	XO/XX	< 20	...	...	...		> 45	~ 24	5.2– 6.6	5.7– 8.1	...
54	E. H.[g]	XX	~ 10	1.0	0	1.6		< 6				
								< 6	...	6.0– 7.4	9.6–12.1	1.23
55	G. S.	$XO/XX_R/XX_RX_R$	> 20	9.0	5.7	6.7		> 6 < 24	...	14.4	16.8	1.26
			< 110	14.0	4.2	12.8		< 3				
56	I. P.	XO/XX_D	...	...	...	...		> 45	...	2.3– 4.4	5.9– 9.4	1.79
57	E. B. H.	XO/?	...	3.9	0	0.9		> 45 < 90	...	7.1–11.2	...	2.23
				7.9	11.6	13.6						

[c] All values ≥ 45 mg HMG-20A were considered definitely increased in adults. Normal values for children were < 3 mg HMG-20A.

[d] The range is given when several determinations were made in the same case. Most values were considered to be within the normal range of variation. Within this range many values were low. Some were definitely decreased.

[e] Normal values for the different age groups were: $^1/_2$–4 years 0.54 U/ml (S.D. ± 0.11), 15–20 years 1.06 U/ml (S.D. ± 0.13), 21–75 years 0.85 U/ml (S.D. ± 0.16).

[f] These determinations were performed at two and eight years of age, respectively.

[g] A stimulation test with chorionic gonadotrophins gave a significantly increased excretion in the urine of chemically determined oestrogens.

Patient			External malformations									
No.	Initials	Sex chromosome constitution	Webbing of the neck	Low implantation of hair	Epicanthic folds	Oedema of hands, feet and lower legs at birth	Miscellaneous	Pigmented naevi[a]	Vascular anomalies	Blood pressure,[b] mm Hg	Kidneys and ureters
1	M.G.	XO	+	—	—	+	Luxation of the left subluxation of the right hip joint.	—	—	...	Bilateral, double renal pelvis.
2	S.B.	XO	+	—	+	+	Pyloric stenosis. Blue sclerae.	—	Small haemangioma to the left in the forehead.	...	—
3	H.G.	XO	+	—	—	+	Blue sclerae.	—	Haemangioma of the upper eye-lids.	...	—
4	M.L.	XO	+	+	—	+	—	...	...	110/50	...
5	I.B.J.	XO	+	+	+	+	Persisting oedema on the right foot.	+	—	135/85	Cleft left renal pelv
6	I.M.L.	XO	—	—	—	—	—	—	—	130/90	—
7	M.B.	XO	—	—	—	—	—	—	—	135/75	Double left renal pelvis and ureters, partly cleft left kidney.
8	I.B.H.	XO	+	+	—	—	—	—	...	...	Malrotated right kidney.
9	V.G.	XO	+	+	+	+	—	+	—	130/80	Cleft right renal pelvis.
10	L.J.	XO	+	+	—	—	—	+ +	—	115/80	Horse shoe kidney with bilateral double renal pelvi and ureters.
11	M.O.	XO	+	+	+	+	Blue sclerae.	+	Lymphangioma of the right foot.	175/85	Horse shoe kidney.
12	B.G.	XO	—	+	—	—	—	+ +	—	125/80	Bilaterally malrotate kidneys.
13	K.A.	XO	—	+	—	—	—	+	—	130/85	Bilateral double renal pelvis.

Malformations studied radiologically											Intelligence quotient	
Sella turcica[d]	Vertebral column	Pelvis[e]	Changes in the knee joint epiphyses[f]	Short fourth metatarsal bones[g]	Changes in the elbow joint epiphyses[h]	Changes of shoulder, radius, ulna and carpal bones	Short fourth metacarpal bones[i]	Height of the palate arch, mm	Audiometric analyses		CVB	SRB
—	...	...	— —	— —		—	— —	...	...		...	...
—	—	—	— —	— —	...	...	...	...	Probably within normal limits.		...	...
...	—	...	— —	— —	— —	—	— —	...	Within normal limits.		...	...
—	...	...	...	...	— —	—	— —	...	...		...	...
—	—	+	+ +	+ —	+ +	...	+ +	16.0	Bilateral, symmetrical, perceptive hearing impairment, "dip", 250–4000 c/s, max. 1000 c/s and 45 dB. Parents within normal limits.		102	123
+ +	—	+	+ +	— —	+ +	S-shaped radius bilaterally.	— —	14.7	Bilateral, perceptive hearing impairment, "dip", 250–4000 c/s, max. 1000 c/s and 20 dB on the right side, max. 2000 c/s and 25 dB on the left side. Mother within normal limits. Father conductive hearing impairment.		81	75
...	—	+	— —	+ —	+ +	...	+ +	14.5	Within normal limits.		72	61
—	...	...	+ +	+ +	...	Short fourth toe bilaterally.	+ ...	...	...		...	...
—	—	+	+ +	+ —	+ +	—	+ +	17.6	Slowly progressive, bilateral, symmetrical, perceptive, "basin-shaped", hearing impairment, 500–2000 c/s, max. 35–40 dB. Parents within normal limits.		83	72
—	—	—	+ —	+ —	— —	...	+ +	17.7	Moderate, conductive hearing impairment on the right, normal on the left side.		88	90
+	Fused second and third cervical vertebrae.	—	+ +	— —	+ +	Inferior angle of the left scapula was missing.	+ +	17.3	Slight conductive hearing impairment on the left, normal on the right side. Mother slight conductive hearing impairment on the right side.		79	72
+	Fused fifth and sixth cervical vertebrae.	—	+ +	+ +	+ +	...	+ +	13.9	...		89	94
—	—	—	+ +	— —	+ +	...	+ +	16.7	Within normal limits.		131	112

Table 17 (*continued*)

Patient			External malformations									
No.	Initials	Sex chromosome constitution	Webbing of the neck	Low implantation of hair	Epicanthic folds	Oedema of hands, feet and lower legs at birth	Miscellaneous	Pigmented naevi[a]	Vascular anomalies	Blood pressure,[b] mm Hg	Kidneys and ureters
14	L.L.	XO	—	+	—	...	—	+ +	—	120/80	Bilateral, double re nal pelvis and ureters.
15	I.O.	XO	—	+	+	—	—	+	Aberrant right subclavian artery (*arteria lusoria*).	125/75	Bilateral, double re pelvis, the lower ones malrotated. Horse shoe kidne
16	C.L.	XO	—	+	...	—	—	+	...	...	...
17	B.H.	XO	+	+	+	—	—	+ +	—	130/85	—
18	I.L.	XO	—	—	—	—	—	+	—	140/90	—
19	K.S.	XO	+	+	...	...	—	...	—	125/90	...
20	B.L.	XO	—	+	—	—	Bilateral myopia, degree of five dioptres. Some missing permanent teeth.	—	—	140/90	Horse shoe kidney.
21	D.F.	XO	—	+	—	—	Blue sclerae.	+	—	130/85	Bilateral, cleft rena pelvis.
22	I.H.	XO	—	+	—	—	Gibbus.	+	—	120/75	—
23	S.I.H.	XO	+	+	+	—	Vitiligo. Spontaneous nystagmus. Converging strabismus of the left eye.	+ +	—	125/80	Double left renal p vis, the upper wa out of function.
24	I.A.	XO	—	+	—	+	Ptosis of the left eyelid and strabismus of the left eye.	+ +	—	170/115	Double left renal p vis and ureter, t lower pelvis was malrotated.
25	B.A.	XO	—	—	—	—	Vitiligo.	—	—	135/90	—

Malformations studied radiologically											Intelligence quotient	
Sella turcica[d]	Vertebral column	Pelvis[e]	Changes in the knee joint epiphyses[f]	Short fourth metatarsal bones[g]	Changes in the elbow joint epiphyses[h]	Changes of shoulder, radius, ulna and carpal bones	Short fourth metacarpal bones[i]	Height of the palate arch, mm	Audiometric analyses	CVB	SRB
+	—	—	+ +	—	+ ...	...	+ ...	20.3	Within normal limits.	104	102
—	—	—	— —	— —	+ +	Short forearms, S-shaped radius bilaterally.	— —	18.7	Within normal limits.	115	102
...	...	...	— ...	— ...	+ ...	Short ulnae.[j]	— ...	...	...	...	...
—	—	—	+ +	— —	...	—	— —	18.0	Within normal limits, parents and sibs within normal limits.	117	108
—	—	—	+ —	— —	+ +	Underdeveloped scapulae. Short ulnae.[j]	+ +	16.0	Bilateral, symmetrical, perceptive hearing impairment, "dip", with a questionable conductive component, 500–2000 c/s, max. 1000 c/s, 35–40 dB.	83	78
—	...	...	...	...	...	...	+ ...	21.8	Within normal limits.	...	...
—	—	—	— —	— —	+ +	Somewhat short ulnae.	— —	16.9	Bilateral, perceptive hearing impairment, "dip", 125–4000 c/s, max. 1000 c/s and 30 dB on the left and 45 dB on the right side.	119	121
—	Underdeveloped distal part of the sacrum Mb Scheuerman	—	+ +	— —	+ +	Somewhat short ulnae. Bilaterally S-shaped radius.	—	20.5	Slight, perceptive high tone loss above 6000 c/s on the right side, and moderate, perceptive hearingimpairment,"flat loss", 30 dB onthe left.	92	90
—	Large thoracic kyphoscoliosis.[k]	—	+ +	+ —	+ +	—	+ +	20.2	Bilateral, symmetrical, perceptive hearing impairment, "dip" with a questionable conductive component, 125–4000 c/s, max. 500–1000 c/s, 50–55 dB.	76	71
—	Underdeveloped atlas and dens epistropheus. Fused second and third cervical vertebrae.	—	+ +	— —	— —	S-shaped ulnae. Underdeveloped caput humeri.	— —	15.8	Pronounced perceptive hearing impairment, sloping on the left side and pronounced perceptive hearing impairment with slight conductive involvement on the right side.	104	103
+	—[k]	—	+ +	+ +	+ +	—	+ +	13.6	Bilateral, perceptive hearing impairment, "dip", on the right side, 250–3000 c/s, max. 1000 c/s, 45 dB, on the left side 250–3000 c/s, max. 2000 c/s, 40 dB.	85	75
+	—	—	+ +	— —	+ +	—	+ +	15.7	...	124	105

Table 17 (*continued*)

Patient			External malformations									
No.	Initials	Sex chromosome constitution	Webbing of the neck	Low implantation of hair	Epicanthic folds	Oedema of hands, feet and lower legs at birth	Miscellaneous	Pigmented naevi[a]	Vascular anomalies	Blood pressure,[b] mm Hg	Kidneys and ureters
26	B.S–n.	XO	—	...	—	—	Paralysis of the abducens nerve. Bilateral hyperopia, degree of three dioptres.	+ +	Coarctation of the aorta.	140/100	—
27	R.L.	XO	+	+	—	—	—	—	—	155/90	—
28	V.S.	XO	—	+	—	—	—	—	—	135/90	—
29	G.A.	XO	+	+	+	—	Some persisting decedious teeth.	+	Coarctation of the aorta.	145/100	—
30	G.K.	XO	+	+	+	+	Ptosis of the right eye-lid.	+	—	145/95	Malrotated kidneys, probably horse shoe kidney.
31	A.F.	XO	—	+	—	—	Unclarified malformation of the brain. Alternating strabismus, scandic speach, tics, astigmatism and hyperopia degree of seven dioptres on the right side and five on the left.	—	—	150/115	—
32	M.N.	XO	—	+	—	—	—	—	—	140/90	Left cleft renal pelv the lower malrotated.
33	M.S.L	XO	—	—	—	—	Strabismus of the left eye.	+	—	130/95	—
34	V.P.	XO	—	—	—	—	—	—	—	130/80	Right cleft and left double renal pelv the lower malrotated.
35	I.J.	XO	—	—	—	...	—	+ +	Small lymphangioma of the lower lip.	180/115	Conglomerate kidn on the right side, no left kidney visible.
36	Y.L.	XX_I	—	—	—	—	—	+	Aberrant right subclavian artery (*arteria lusoria*)	120/75	—
37	G.E.	XO/XX_I	—	+	—	—	Strabismus of the left eye.	+	—	130/85	—

Malformations studied radiologically											Intelligence quotient	
Sella turcica[d]	Vertebral column	Pelvis[e]	Changes in the knee joint epiphyses[f]	Short fourth metatarsal bones[g]	Changes in the elbow joint epiphyses[h]	Changes of shoulder, radius, ulna and carpal bones	Short fourth metacarpal bones[i]	Height of the palate arch, mm	Audiometric analyses	CVB	SRB
+	Spina bifida in sacrum. Malformed coccyx. Myelomeningocele.	—	+ ...	—...	...	...	—...	...	...	...	...
...	—	—	— —	+ —	— —	Bilaterally S-shaped radius.	— —	17.3	Within normal limits.	108	105
+	Partially fused fifth and sixth cervical vertebrae.	—	+ +	+ +	+ ...	Short ulnae.	+ +	16.2	Slight, bilateral, conductive hearing impairment.	76	70
...	Thoracic kyphoscoliosis.	—	+ +	— —	+ +	—	+ +	16.0	Mixed, bilateral moderate hearing impairment. Parents within normal limits.	97	90
—	Infantile.	—	+ +	— —	+ +	Short right ulna.[j]	+ —	16.8	Bilateral, symmetrical, perceptive hearing impairment above 2000c/s.	97	103
—	—	—	+ +	— —	— —	The styloid processes of the ulnae were missing.[k]	+ +	17.4	...	76	73
—	—	—	+ +	+ —	+ +	—	— —	17.9	...	88	86
—	Underdeveloped sacrum, malformed coccyx.	—	— —	+ +	...	—	+ ...	...	Slight, bilateral, perceptive high tone loss above 6000 c/s.	...	...
—	—	—	— —	+ +	+ +	Short forearms.[j]	+ +	20.2	Bilateral, symmetrical, perceptive hearing impairment, "dip", 250–4000 c/s, max. 2000 c/s, 35 dB.	80	70
—	—	—	+ +	— —	+ +	Bilaterally S-shaped radius.[j]	+ —	19.5	Pronounced, perceptive hearing impairment 60 dB on the left side. Excessive, mixed hearing impairment 80 dB on the right side.	104	111
—	—	—	+ +	+ —	+ +	—[j]	+ +	15.2	Bilateral, symmetrical, perceptive hearing impairment, "dip", 250–3000 c/s, max. 1000 c/s, 40–45 dB.	109	108
—	Underdeveloped distal part of sacrum.	—	— —	+ +	+ +	—	+ +	17.3	Bilateral, perceptive hearing impairment, "dip", 500–4000 c/s, max. 2000 c/s, on the right 25 dB, and on the left side 35 dB.	108	100

Table 17 (*continued*)

Patient			External malformations						Vascular anomalies	Blood pressure,[b] mm Hg	Kidneys and ureters
No.	Initials	Sex chromosome constitution	Webbing of the neck	Low implantation of hair	Epicanthic folds	Oedema of hands, feet and lower legs at birth	Miscellaneous	Pigmented naevi[a]			
38	B.J.	XO/XX_I	—	+	—	—	Slight converging strabismus on the left side.	—	—	130/90	Left cleft renal pelvis
39	B.S.	XO/XX_I	—	+	—	—	—	—	—	130/70	—
40	A.S.	XO/XX_I	—	—	—	—	—	+	—	110/75	—
41	L.A.	XO/XX_I	—	—	—	—	Progressive cerebellar degeneration. Slight part exophtalmus.	—	—	115/80	Conglomerate kidney on the left side, the lower part malrotated. Normal right kidney.
42	C.S.	XO/XX_I	—	+	—	—	Persisting deciduous teeth.	+	—	125/85	—
43	E.S.	XO/XX_I $XX_I\,X_I$	—	—	—	—	—	—	—	130/80	...
44	M.A.	XX_I	—	—	—	—	—	+ +	—	130/90	—
45	M.J.	XO/XX_I	—	...	—	...	Areate alopecia.	—	—	150/90	...
46	R.K.	XO/XX_I	—	+	—	...	—	+ +	—	140/90	Probable horse shoe kidney, double right renal pelvis and ureters.
47	M.C.	XO/XX	—	...	+	—	Slight ptosis of the right eye-lid.	+	—	145/80	...
48	S.S.	XO/XX	+	+	+	—	—	+	...	125/70	...
49	B.N.	XO/XX	—	—	—	—	Spontaneous nystagmus.	—	—	130/90	—
50	A.H.	XO/XX	—	—	—	—	—	+	—	120/80	—

Malformations studied radiologically												Intelligence quotient	
Sella turcica[d]	Vertebral column	Pelvis[e]	Changes in the knee joint epiphyses[f]	Short fourth metatarsal bones[g]	Changes in the elbow joint epiphyses[h]	Changes of shoulder, radius, ulna and carpal bones	Short fourth metacarpal bones[i]	Height of the palate arch, mm	Audiometric analyses	CVB	SRB
–	—[k]	—	– –	– –	+ +	—	– –	16.7	...	99	102
+ +	—	—	+ +	+ —	+ +	Short scapulae.[j]	– –	18.2	Slight, conductive hearing impairment on the left, within normal limits on the right side.	109	111
—	—	—	– –	– –	+ +	Short ulnae.[j]	+ +	16.0	Within normal limits. Mother within normal limits.	96	100
—	Infantile.	+	+ +	+ —	+ +	Short ulnae.	+ +	17.3	Bilateral, symmetrical, perceptive hearing impairment, "flat loss", 50–60 dB.	92	87
—	Thoracic kyphosis. Two fractures.	—	+ +	– –	+ +	Bilaterally S-shaped radius and ulna. Short ulnae.	– –	14.0	Within normal limits.	96	96
—	—[k]	—	+ +	– –	– –	Short ulnae.[j]	+ +	17.6	Pronounced, bilateral, perceptive hearing impairment: On the right side, "flat loss", 75–80 dB, on the left side "abrupt hearing loss" above 250–500 c/s, "flat loss", above 500 c/s, 40–60 dB.	120	114
—	—	—	+ +	+ +	+ +	—	+ +	15.2	Bilateral, symmetrical, perceptive hearing impairment, "flat loss", 35 dB.	90	102
—	...	—	—...	—...	—...	...	+ +	...	...	...	...
—	—	—	+ +	– –	– –	Bilaterally short radius and ulna.	+ +	14.0	Within normal limits.	117	114
...	...	...	—...	—...	+ ...	—	—...	18.0	...	112	103
...	...	...	+ ...	...	...		—...	...	...	...	...
...	—	—	– –	– –	– –	—	– –	...	Within normal limits on the left side. On the right side perceptive hearing impairment, "dip", max. 1000 c/s, 35 dB. Conductive component shown in audiogram probably measurement artefact.	92	99
– –	—	—	– –	+ +	+ +	—	+ +	...	Slight, conductive hearing impairment on the right, normal on the left side.	113	105

Table 17 (*continued*)

Patient			External malformations									
No.	Initials	Sex chromosomic constitution	Webbing of the neck	Low implantation of hair	Epicanthic folds	Oedema of hands, feet and lower legs at birth	Miscellaneous	Pigmented naevi[a]	Vascular anomalies	Blood pressure,[b] mm Hg	Kidneys and ureters
51	M.H.	XO/XX	—	+	—	—	Same persisting deciduous teeth.	—	—	125/70	Horse shoe kidney, with bilateral, clef renal pelvis.
52	E.K.	XO/XX	—	—	—	—	—	+	—	130/85	—
53	S.Ö.	XO/XX	—	...	—	...	Uneven pigmentation of the skin.	—	—	130/80	Horse shoe kidney with bilateral, clef renal pelvis.
54	E.H.	XX	+	+	—	—	Mb Raynaud. Probably nervous anorexia. Bilateral ptosis. Hypertelorism.	—	—	110/65	—
55	G.S.	$XO/XX_R/XX_RX_R$	—	—	—	—	—	—	—	125/80	Double, left renal pelvis and ureters.
56	I.P.	XO/XX_D	—	+	—	—	—	—	—	135/80	Horse shoe kidney.
57	E.B.H.	XO/?	—	+	—	—	Converging strabismus. Hyperopia, degree of four dioptres on both sides.	—	—	125/80	—

[a] − = apparently normal number of pigmented naevi. + = apparently increased number of pigmented naevi. + + = increased number of pigmented naevi.

[b] The values given generally represent several examinations.

[c] − = normal skeletal structure. + = slightly dysplastic skeletal structure. + + = dysplastic skeletal structure.

[d] − = apparently normal sella turcica. + = apparently small sella turcica. + + = apparently small sella turcica overbridged by bone.

[e] − = normal pelvis. + = infantile pelvis.

[f] − − = bilaterally normal epiphyses. + − = unilateral changes of the epiphyses. + + = bilateral changes of the epiphyses.

Malformations studied radiologically										Audiometric analyses	Intelligence quotient	
Sella turcica[d]	Vertebral column	Pelvis[e]	Changes in the knee joint epiphyses[f]	Short fourth metatarsal bones[g]	Changes in the elbow joint epiphyses[h]	Changes of shoulder, radius, ulna and carpal bones	Short fourth metacarpal bones[i]	Height of the palate arch, mm			CVB	SRB
+ +	—	—	— —	+ —	+ +	Bilaterally underdeveloped scapulae, and short S-shaped radius.[j]	+ +	14.1		...	...	...
...	—	—	— —	+ —	+ +	Somewhat short ulnae bilaterally.	+ +	17.0		Bilateral, symmetrical, perceptive hearing impairment, "dip", 250–4000 c/s, max. 1000 c/s, 40 dB.	103	88
—	—[k]	—	+ ...	...	+ +	—	+ ...	...		Slight bilateral perceptive hearing impairment above 6000 c/s.	...	...
—	S-shaped thoracic scoliosis. Fused vertebrae lower thoracic region.	Underdeveloped distal sacrum and hip joints. Horizontal sacrum.	+ +	— —	+ +	Missing styloid process of ulnae.[m]	+ +	19.6		...	98	100
+	—[k]	Spina bifida of, three sacral vertebrae.	— —	+ —	+ +	—	+ +	17.4		Within normal limits.	81	71
—	Underdeveloped distal sacrum and coccyx.	—	+ —	— —	— —	Lunatum and triquetrum were fused on the right side.	— —	18.2		Bilateral, symmetrical, perceptive hearing impairment, "dip", 125–4000 c/s, max. 1000 c/s, 60 dB. Father slight, bilateral perceptive hearing impairment, "gradual loss", mother and brother within normal limits.	86	84
—	—	—	+ +	— —	+ +	—	— —	15.9		...	100	103

[g] — — = normal length of the fourth metatarsal bones. + — = short fourth metatarsal bone on one side. + + = short fourth metatarsal bones on both sides.

[h] — — = normal epiphyses. + — = unilateral changes of the epiphyses. + + = bilateral changes of the epiphyses.

[i] — — = normal length of the fourth metacarpal bones. + — = short fourth metacarpal bone on one side. + + = short fourth metacarpal bones on both sides.

[j] Underdeveloped ulnar part of the distal radial epiphyses and the radial part of the distal ulnar epiphyses.

[k] The cervical part of the vertebral column was not examined.

[l] Malformed acetabulum of the left shoulder joint.

[m] Fusion of the bones multangulum majus, naviculare and triquetrum, lunatum.

TABLE 18. *Data regarding physical growth*

Patient			At birth		At the last examination								Oestrogen therapy: Age of	
						Age								
No.	Initials	Sex chromosome constitution	Weight, g	Length, cm	Difference between calculated and actual date of birth,[a] days	Chronological, years	Skeletal,[b] years	Epiphyseal zones[c]	Weight, kg	Height, cm	Span, cm	Lower measurement, cm	Onset, years	Withdrawal, years
1	M.G.	XO	3190	46	−7	$7\frac{5}{12}$	±0	Open	5.270	62	60	21	—	—
2	S.B.	XO	3730	49	±0	$7\frac{5}{12}$	±0	Open	6.940	68	62	29	—	—
3	H.G.	XO	2550	47	−10	$17\frac{5}{12}$	±0	Open	9.800	78	76	32	—	—
4	M.L.	XO	3050	48	—	8	−1–2	Open	20.3	111	...	...	...	...
5	I.B.J.	XO	3250	49	+4	16	±0	Open	37.0	138	132	67	—	—
6	I.M.L.	XO	2820	49	...	16	−3	Open	31.0	130	132	66	—	—
7	M.B.	XO	3480	50	—	17	±0	Open	54.0	147	141	72	$17\frac{3}{12}$	—
8	I.B.H.	XO	2500	48	−7	17	...	...	46.3	144	...	...	...	...
9	V.G.	XO	2850	47	−15	18	−2	Open	41.0	144	150	69	$17\frac{11}{12}$	—
10	L.J.	XO	2650	45	+9	18	±0	Closing	47.3	142	140	72	$17\frac{11}{12}$	—
11	M.O.	XO	2900	49	−5	18	−2	Open	40.7	137	139	69	$18\frac{1}{12}$	—
12	B.G.	XO	3300	50	—	18	−2	Open	42.0	144	142	72	$18\frac{7}{12}$	—
13	K.A.	XO	3150	51	−8	18	−2	Closing	35.5	135	135	70	$17\frac{2}{12}$	—
14	L.L.	XO	...	...	...	19	±0	Closing	47.5	145	143	72	$19\frac{5}{12}$	—
15	I.O.	XO	3150	48	−3	19	+1	Closed	47.7	141	128	63	$12\frac{0}{12}$	—
16	C.L.	XO	3000	48	−4	19	±0	Closing	38.0	140	...	...	...	...
17	B.H.	XO	3750	52	—	20	±0	Closed	53.2	152	157	78	$17\frac{7}{12}$	—
18	I.L.	XO	2960	48	−31	20	±0	Closed	53.0	142	144	69	$17\frac{8}{12}$	—
19	K.S.	XO	3050	46	—	21	...	...	82.5	151	169	78	$18\frac{6}{12}$	—
20	B.L.	XO	2840	48	−1	21	±0	Closing	48.0	145	143	71	$15\frac{9}{12}$	—
21	D.F.	XO	2870	49	−17	23	⩾0	Closed[d]	55.5	141	150	72	$15\frac{2}{12}$	$17\frac{4}{12}$
22	I.H.	XO	3970	52	−7	23	−3	Closed[d]	47.5	139	153	78	$20\frac{9}{12}$	—
23	S.I.H.	XO	2800	...	—	24	⩾0	Closed[d]	51.0	149	150	73	$17\frac{0}{12}$	$23\frac{5}{12}$
24	I.A.	XO	2500	45	—	24	⩾0	Closed[d]	49.0	134	133	64	$17\frac{4}{12}$	$23\frac{5}{12}$
25	B.A.	XO	3315	49	+13	24	⩾0	Closed[d]	50.3	148	143	72	—	—
26	B.S-n.	XO	2190	42	−43	25	...[e]	...	41.5	136	135	63	$17\frac{3}{12}$	$21\frac{7}{12}$
27	R.L.	XO	...	...	...	26	⩾0	Closed[d]	60.1	155	155	75	$21\frac{3}{12}$	$22\frac{7}{12}$
28	V.S.	XO	2000	42	−26	26	⩾0	Closed	48.7	140	148	70	$23\frac{5}{12}$	$25\frac{6}{12}$
29	G.A.	XO	2020	48	−21	28	⩾0	Closed[d]	57.9	144	145	78	$28\frac{2}{12}$	—
30	G.K.	XO	2540	50	+11	29	⩾0	Closed	32.2	142	144	69	$20\frac{10}{12}$	–
31	A.F.	XO	1750	...	...	29	⩾0	Closed	39.8	139	140	70	$17\frac{11}{12}$	$26\frac{3}{12}$
32	M.N.	XO	...	...	...	29	⩾0[f]	Closed	46.0	145	140	72	$19\frac{10}{12}$	$28\frac{11}{12}$
33	M.S.L.	XO	3320	50	−5	30	...[g]	...	52.0	146	144	73	$17\frac{3}{12}$	$27\frac{8}{12}$
34	V.P.	XO	...	...	...	35	⩾0	Closed	45.0	135	129	65	$21\frac{6}{12}$	$28\frac{3}{12}$
35	I.J.	XO	...	...	...	42	⩾0	Closed	69.9	144	145	69	—	—
36	Y.L.	XX_I	2760	47	—	16	−1	Open	34.2	132	133	68	—	—
37	G.E.	XO/XX_I	2815	48	—	17	+2–3[h]	Closed	42.2	142	137	58	$13\frac{2}{12}$	—
38	B.J.	XO/XX_I	3090	50	±0	18	−1	Open	43.5	139	149	70	$18\frac{0}{12}$	—
39	B.S.	XO/XX_I	2830	48	−3	18	−2–3[i]	Open	39.0	139	140	70	$18\frac{11}{12}$	—

Table 18 (*continued*)

No.	Patient: Initials	Patient: Sex chromosome constitution	At birth: Weight, g	At birth: Length, cm	Difference between calculated and actual date of birth,[a] days	At the last examination: Age: Chronological, years	At the last examination: Age: Skeletal,[b] years	At the last examination: Epiphyseal zones[c]	At the last examination: Weight, kg	At the last examination: Height, cm	At the last examination: Span, cm	At the last examination: Lower measurement, cm	Oestrogen therapy: Age of: Onset, years	Oestrogen therapy: Age of: Withdrawal, years
40	A.S.	XO/XX_I	2940	47	−1	18	+1[j]	Closed	34.0	138	135	66	$14\frac{10}{12}$	—
41	L.A.	XO/XX_I	1980	43	−45	19	+0	Closing	40.0	141	140	72	$17\frac{5}{12}$	$18_{\overline{12}}$
42	C.S.	XO/XX_I	3300	...	—	19	±0	Closed	51.5	145	145	71	$15\frac{1}{12}$	—
43	E.S.	XO/XX_I $XX_I X_I$	3100	48	−2	23	⩾0[k]	Closed	79.3	149	146	71	$14\frac{11}{12}$	~20
44	M.A.	XX_I	1660	43	—	25	⩾0	Closed[l]	38.0	135	132	68	$18\frac{3}{12}$	$24\frac{5}{12}$
45	M.J.	XO/XX_I	...	...	...	27	⩾0	Closed[d]	50.5	147	150	74	$16\frac{6}{12}$	~20
46	R.K.	XO/XX_I	...	...	...	29	⩾0	Closed	35.5	134	134	64	$19\frac{11}{12}$	$23\frac{2}{12}$
47	M.C.	XO/XX	3410	50	−1	17	±0	Closing	53.5	150	150	74	$17\frac{11}{12}$	—
48	S.S.	XO/XX	2360	49	−15	17	+1	Closing	39.6	136	...	...	$13\frac{5}{12}$	$14\frac{2}{12}$
49	B.N.	XO/XX	3710	52	+11	18	±0	Closing	40.4	152	164	81	$18\frac{5}{12}$	—
50	A.H.	XO/XX	3400	47	−5	20	−1	Closing	55.0	154	153	83	$17\frac{5}{12}$	$17\frac{11}{12}$
51	M.H.	XO/XX	2200	46	−13	22	⩾0	Closed	48.4	148	142	73	$16\frac{7}{12}$	—
52	E.K.	XO/XX	3300	50	+1	33	⩾0	Closed[d]	51.0	153	156	76	$32\frac{10}{12}$	—
53	S.Ö.	XO/XX	...	...	...	35	⩾0	Closed[d]	47.3	139	150	70	$32\frac{4}{12}$	—
54	E.H.	XX	2630	42	−13	18	+2–3	Closed	27.5	142	142	72	—	—
55	G.S.	$XO/XX_R/$ $XX_R X_R$	2480	47	+19	22	⩾0	Closed	47.5	143	140	70	$20\frac{7}{12}$	$21\frac{5}{12}$
56	I.P.	XO/XX_D	...	...	...	23	⩾0[m]	Closed	37.0	137	138	68	$14\frac{6}{12}$	—
57	E.B.H.	XO/?	...	...	...	21	−1–2	Closed	44.5	139	146	70	$16\frac{7}{12}$	$17\frac{8}{12}$

[a] + = pregnancy and parturition were normal, but no exact date could be found for the mother's last menstruation.

[b] ±1 year was considered as the normal variation.

[c] The terms "open", "closing" and "closed" refer only to the distal femoral and proximal tibial epiphyses. "Open" zones indicated normal width, "closing" decreased width and "closed" absence of the cartilaginous zones as seen on X-ray examination.

[d] All epiphyses were closed except that of the iliac crest which was completely or partly open. Sometimes it was difficult to judge whether there were epiphyses at the iliac crests or not.

[e] At the age of 12 years her skeletal age was ±0 years and at 18 it was +1 year.

[f] At the age of 19 years her skeletal age was −2 years.

[g] Earlier investigations at 16, 17, 18 and 19 years of age showed a constant skeletal age of +1 year.

[h] At the age of 14 years her skeletal age was ±0 years.

[i] At the age of 15 years her skeletal age was +2 years.

[j] At the age of 14 years her skeletal age was ±0 years.

[k] At the age of 15 years her skeletal age was ±0 years.

[l] All epiphyses were closed except those of the acromion, the distal radius and the iliac crest.

[m] Eearlier investigations showed the following skeletal ages, at 12 years of age ±0, and at 14 and 15 years of age +2 years.

TABLE 19. *Data on blood groups, serum protein groups and ability to taste phenylthiocarbamide.*

Patient[a]			Blood group								Serum protein group			
No.	Initials and parents[b]	Sex chromosome constitution	ABO	MNS	Rhesus	P	Kell	Duffy, Fy (a)	Lewis, Le (a)	Xg (a)	Hapto-globins, Hp	Gc	Gm (a)	Ability to taste phenyl-thiocarbamide[c]
1	M. G.	XO	B	MS+	$Rh_1\ Rh_2$	—	—	+	+	+	1–1	2–1	+	...
	M	...	B	MS+	Rh_1 rh	...	—	...	...	+	...	...	...	...
	F	...	O	MNS–	$Rh_2\ Rh_2$	...	—	...	...	—	...	...	...	...
2	S. B.	XO	B	MNS–	Rh_1^W rh	—	—	+	+	+	2–1	1–1	—	...
	M	...	O	MNS–	$Rh_1^W\ Rh_1$	—	—	+	+	+	2–2	1–1	—	...
	F	...	B	MN...	Rh_1 rh	...	...	...	...	+	...	...	...	...
3	H. G.	XO	O	MNS+	Rh_1 rh	+	—	+	+	+	2–2	1–1	...	...
	M	...	A_2	NS–	Rh_2 rh	+	—	—	—	+	2–1	1–1	+	...
	F	...	A_1	MNS+	Rh_1 rh	...	+	...	...	+	...	...	...	...
5	I. B. J.	XO	O	MNS–	$Rh_1\ Rh_1$	...	—	...	...	+	...	...	...	T
	M	...	O	NS–	Rh_1 rh	...	—	...	...	+	...	...	...	...
	F	...	O	MS–	Rh_1 rh	...	—	...	...	+	...	...	...	...
6	I. M. L.	XO	A_2B	MNS–	rh	...	—	...	...	—	...	...	...	T
	M	XX	B	MNS+	Rh_1 rh	...	—	...	...	+	...	...	...	...
	F	XY	A_2	NS–	Rh_2 rh	...	—	...	...	+	...	...	...	...
7	M. B.	XO	A_1	NS–	Rh_1 rh	+		+	—	+	2–2	2–1	+	T
	M	...	A_1	NS–	Rh_2 rh	...	—	...	...	+	...	...	...	...
	F	...	O	NS–	Rh_1 rh	...	—	...	...	+	...	...	...	...
9	V. G.	XO	O	MS–	Rh_2 rh	—	—	+	—	+	2–1	1–1	—	T
	M	XX	O	MNS	Rh_2 rh	...	—	...	...	—	...	...	...	...
	F	XY	A_1	MS–	Rh_1 rh	...	—	...	...	+	...	...	...	...
10	L. J.	XO	A_2B	MS–	$Rh_1\ Rh_1$	+	—	+	—	+	2–1	1–1	—	T
	M	...	A_2	MNS–	$Rh_1\ Rh_1$	+	—	+	—	+	2–2	2–1	—	...
	F	...	B	MNS–	$Rh_1\ Rh_2$	...	—	...	...	+	...	...	...	...
11	M. O.	XO	O	MS+	Rh_1 rh	—	+	+	+	+	2–1	1–1	+	T
	M	...	O	MS+	rh	...	—	...	...	+	...	...	...	...
	F	...	A_1	MS–	Rh_1 rh	...	+	...	...	—	...	...	...	...
12	B. G.	XO	A_2	MNS–	$Rh_1^W\ Rh_1$	+	—	—	—	—	2–2	2–1	+	...
	M	...	B	MNS+	Rh_1 rh	—	—	+	—	+	2–1	2–1	+	...
	F	...	A_1	MS–	Rh_1 rh	...	—	...	...	—	...	...	...	...
13	K. A.	XO	A_2	MS–	Rh_1 rh	...	—	+	—	+	...	1–1	+	T
	M	...	A_1	MS+	rh	...	—	...	...	+	...	...	...	...
	F	...	O	MS–	Rh_1 rh	...	—	...	...	—	...	...	...	...
14	L. L.	XO	A_1	MNS+	Rh_1 rh	—	—	+	—	...	2–2	1–1	+	T
15	I. O.	XO	A_1	MNS+	Rh_1 rh	...	—	—	—	+	2–2	1–1	+	t
	M	...	A_1	MNS+	rh	...	—	...	...	+	...	...	...	...
	F	...	B	MNS+	Rh_1 rh	...	+	...	...	—	...	...	...	...
17	B. H.	XO	B	MNS+	Rh_1 rh	+	—	+	—	+	2–2	1–1	—	T
	M	...	B	MNS–	rh	...	—	...	...	+	...	...	...	...
	F	...	B	MNS+	$Rh_1\ Rh_1$	...	—	...	...	—	...	...	...	...

Table 19 (*continued*)

Patient[a]			Blood group								Serum protein group				
No.	Initials and parents[b]	Sex chromosome constitution	ABO	MNS	Rhesus	P	Kell	Duffy, Fy (a)	Lewis, Le (a)	Xg (a)	Haptoglobins, Hp	Gc	Gm (a)	Ability to taste phenylthiocarbamide[c]
18	I. L.	XO	O	MNS −	$Rh_1\ Rh_2$	+	—	—	—	+	...	...	...	T
	M	...	A_1	MNS +	$Rh_1\ Rh_2$	+	—	...	...	+	...	...	...	...
	F	...	O	MNS +	$Rh_1\ Rh_1$	+	—	...	...	—	...	...	...	...
19	K. S.	XO	A_1	MNS −	Rh_1 rh	+	—	+	—	...	2–2	1–1	—	T
20	B. L.	XO	O	MNS −	Rh_2 rh	...	—	...	...	+	...	...	...	T
	M	...	B	MS −	Rh_1 rh	...	—	...	...	+	...	...	...	...
	F	...	A_1	MNS +	$Rh_1\ Rh_1$	...	—	...	...	+	...	...	...	...
21	D. F.	XO	O	MS +	rh	...	—	+	—	+	2–1	1–1	—	T
	M	...	O	MNS +	Rh_1 rh	...	—	...	...	+	...	...	...	...
22	I. H.	XO	A_1	MNS +	Rh_1 rh	+	—	+	—	+	2–1	2–1	—	T
	M	...	A_1	MS +	$Rh_1\ Rh_1$	...	—	...	...	+	...	...	...	...
	F	...	A_1	NS −	rh	...	—	...	...	+	...	...	...	...
23	S. I. H.	XO	A_1	MNS +	$Rh_1\ Rh_2$	+	—	+	...	+	2–1	1–1	+	T
	M	...	O	MNS +	$Rh_1\ Rh_1$	...	—	...	...	+	...	...	...	...
	F	...	A_1	MNS −	Rh_2 rh	...	—	...	...	—	...	...	...	...
24	I. A.	XO	B	NS −	Rh_1 rh	+	—	+	—	...	2–1	1–1	+	...
25	B. A.	XO	O	MNS −	rh	+	—	+	—	...	1–1	2–1	+	T
26	B. S-n.	XO	A_1	MNS −	$Rh_1\ Rh_2$	—	—	+	—	...	2–1	1–1	-	...
	M	...	A_1	MS +	$Rh_1\ Rh_1$	—	+	+	—	...	2–1	1–1	+	...
27	R. L.	XO	A_1	NS −	$Rh_1\ Rh_2$	+	—	—	—	...	2–1	1–1	—	T
28	V. S.	XO	O	MNS −	Rh_1 rh	+	—	+	—	...	1–1	2–1	+	T
29	G. A.	XO	A_1	MS −	$Rh_1\ Rh_2$	...	—	...	...	+	...	...	...	T
	M	...	A_1	MS −	Rh_2 rh	...	—	...	...	+	...	...	...	...
	F	...	A_1	MNS −	$Rh_1\ Rh_1$	...	—	...	...	—	...	...	...	...
30	G. K.	XO	O	MS +	Rh_2 rh	—	+	+	—	—	2–1	2–1	—	T
	M	...	O	MNS +	Rh_2 rh	+	—	...	...	+	...	...	...	...
	F	...	O	MNS +	$Rh_1\ Rh_2$	—	+	...	...	—	...	...	...	...
31	A. F.	XO	B	NS −	Rh_1 rh	—	—	+	—	+	1–1	2–1	+	T
	M	...	A_2	NS −	Rh_2 rh	+	—	+	—	+	2–1	2–1	+	...
	F	...	B	NS −	$Rh_1\ Rh_1$	...	—	...	...	+	...	...	...	...
	Twin	...	B	NS −	$Rh_1\ Rh_2$	+	—	+	—	...	2–1	2–2	+	...
32	M. N.	XO	O	MS +	$Rh_1\ Rh_1$	+	—	+	—	+	2–1	1–1	—	T
	M	...	B	...	...	...	+	...	...	+	...	...	...	...
	F	...	O	MS −	$Rh_1\ Rh_2$	...	—	...	...	+	...	...	...	...
33	M. S. L.	XO	A_1	MNS +	$Rh_1\ Rh_1$	...	—	—	—	...	1–1	2–1	—	T
34	V. P.	XO	A_1B	MS +	Rh_1 rh	...	—	+	—	...	2–2	2–1	—	T
35	I. J.	XO	A_1	MS −	Rh_1 rh	+	—	+	—	+	1–1	2–2	—	T
	M	...	A_1	MS −	$Rh_1\ Rh_2$	...	—	...	...	+	...	...	...	...
	F	...	A_1	MS −	$Rh_1\ Rh_2$	...	—	...	...	+	...	...	...	...

[a] Certain cases have been excluded from the table because no information was available.

[b] M = mother; F = father.

[c] T = taster; t = non-taster. The frequency of tasters among 228 healthy Swedish students was 83.8% (Dr. *T. Romanus*, Stockholm, personal communication).

[d] The patient's three brothers, her four maternal uncles, her maternal aunt and the maternal grandmother were all Xg(a^+). The maternal grandfather was dead.

Table 19 (*continued*)

Patient[a]			Blood group								Serum protein group			Ability to taste phenyl-thiocarbamide[c]
No.	Initials and parents[b]	Sex chromosome constitution	ABO	MNS	Rhesus	P	Kell	Duffy, Fy (a)	Lewis, Le (a)	Xg (a)	Hapto-globins, Hp	Gc	Gm (a)	
36	Y. L.[d]	XX_I	O	MS −	Rh_1 rh	—	—	+	+	—	2–1	2–1	+	T
	M	···	A_1	MS +	rh	—	—	—	—	+	2–2	2–1	+	···
	F	···	A_1	MS +	Rh_1 rh	+	—	···	···	—	···	···	···	···
37	G. E.	XO/XX_I	O	MS −	Rh_1^W Rh_1	+	—	—	—	+	2–2	1–1	+	T
	M	···	O	MS −	Rh_1 rh	+	—	+	—	+	2–2	1–1	+	···
	F	···	B	MNS +	Rh_1 rh	···	—	···	···	—	···	···	···	···
38	B. J.	XO/XX_I	O	NS +	Rh_1 rh	—	—	+	—	—	1–1	2–1	+	T
	M	···	O	NS +	Rh_1 Rh_1	+	—	···	···	+	···	···	···	···
	F	···	O	MNS +	Rh_1 rh	+	—	···	···	+	···	···	···	···
39	B. S.	XO/XX_I	O	MNS −	Rh_1 Rh_2	+	—	+	—	+	1–1	2–1	—	T
	M	···	A_1	MNS −	Rh_1 rh	···	—	···	···	+	···	···	···	···
	F	···	O	NS −	Rh_1 Rh_2	···	—	···	···	+	···	···	···	···
40	A. S.	XO/XX_I	A_1	MS +	Rh_1 rh	—	—	+	—	—	···	2–1	+	T
	M	XX	O	MNS +	rh	—	—	+	—	+	2–1	1–1	+	···
	F	XY	A_1	MNS +	Rh_1 Rh_1	···	—	···	···	—	···	···	···	···
41	L. A.	XO/XX_I	A_1	MNS +	Rh_2 rh	+	—	+	—	+	2–1	2–1	—	T
	M	XX	A_1	MNS +	Rh_1 Rh_2	···	—	···	···	+	···	···	···	···
	F	XY	O	MNS +	Rh_1 rh	+	—	+	—	—	2–2	2–2	—	···
42	C. S.	XO/XX_I	A_1	MS −	Rh_2 rh	+	—	—	—	+	2–2	1–1	+	T
	M	···	A_1	MNS −	Rh_2 Rh_2	···	—	···	···	+	···	···	···	···
	F	···	A_2	MS −	rh	···	—	···	···	+	···	···	···	···
43	E. S.	$XO/XX_I/XX_IX_I$	A_1	MNS +	Rh_1 rh	+	—	—	—	···	1–1	2–1	—	T
44	M. A.	XX_I	A_1	NS +	Rh_1 Rh_1	+	—	+	—	+	1–1	2–1	—	T
	M	XX	O	NS −	Rh_1 Rh_1	+	—	+	—	+	2–1	2–1	+	···
	F	XY	A_1	NS +	Rh_1^W Rh_2	+	—	+	—	—	1–1	···	—	···
	Twin	XX	O	NS −	Rh_1 rh	···	—	···	···	+	···	···	···	···
46	R. K.	XO/XX_I	A_1	MS +	Rh_1 rh	+	—	—	—	···	1–1	1–1	—	T
47	M. C.	XO/XX	A_1	MNS +	Rh_1 rh	+	—	—	—	···	2–1	2–1	—	t
50	A. H.	XO/XX	O	MS +	Rh_1 Rh_2	+	—	+	—	—	2–2	1–1	+	T
	M	···	A_1	MNS −	Rh_2 rh	···	—	···	···	+	···	···	···	···
	F	···	O	MNS +	Rh_1 rh	···	—	···	···	—	···	···	···	···
53	S. Ö.	XO/XX	A_1	MS +	Rh_1 rh	—	—	+	—	···	2–1	1–1	—	T
54	E. H.	XX	O	MNS +	Rh_1 rh	—	—	+	—	···	2–1	1–1	+	T
	M	···	O	MS +	Rh_1 rh	—	—	+	—	···	2–1	1–1	+	···
55	G. S.	$XO/XX_R/XX_RX_R$	A_1	MNS −	Rh_1 rh	—	+	+	—	···	2–1	2–1	—	T
	F	···	O	MNS −	Rh_2 rh	—	—	—	—	···	2–2	2–1	—	···
56	I. P.	XO/XX_D	A_1	NS −	Rh_1 rh	—	—	—	—	+	1–1	2–2	+	T
	M	···	A_1	MNS +	Rh_1 rh	···	—	···	···	+	···	···	···	···
	F	···	A_1	NS −	rh	···	—	···	···	+	···	···	···	···
57	E. B. H.	XO/?	B	MNS −	Rh_1 rh	—	—	+	—	—	2–2	2–1	—	t
	M	···	B	NS −	Rh_2 rh	···	—	···	···	+	···	···	···	···
	F	···	O	MS −	Rh_1 Rh_2	···	—	···	···	—	···	···	···	···

TABLE 20. *Gynaecological data.*

Patient			Before oestrogen therapy				After oestrogen therapy				Oestrogen therapy: Age of		Menarche		Age at laparotomy[e], years
					Growth of				Growth of						
No.	Initials	Sex chromosome constitution	Menstruation[a]	Breast development[b]	Pubic hair[c]	Axillary hair[d]	Menstruation	Breast development[b]	Pubic hair[c]	Axillary hair[d]	Onset, years	Withdrawal, years	Mother	Sisters	
1	M. G.	XO	—	—	—	—	...	...	...	...	—	—	12	—	—
2	S. B.	XO	—	—	—	—	...	...	...	...	—	—	...	...	—
3	H. G.	XO	—	—	—	—	...	...	...	...	—	—	12	—	—
4	M. L.	XO	—	—	—	—	...	...	...	...	...	...	...	...	—
5	I. B. J.	XO	—	—	+	—	...	...	...	...	—	—	14	14	—
6	I. M. L.	XO	—	—	—	—	...	...	...	...	—	—	17	13–15	—
7	M. B.	XO	—	+	+	+	+	+ +	+	...	17 $\frac{3}{12}$	—	16	—	17
8	I. B. H.	XO	—	—	—	—	...	...	...	...	...	...	...	...	18
9	V. G.	XO	Once	—	+	—	...	...	...	...	17 $\frac{11}{12}$	—	17	—	—
10	L. J.	XO	—	—	...	...	+	+ +	+ +	+	17 $\frac{11}{12}$	—	14	—	—
11	M. O.	XO	—	—	+	+	+	+ +	+ +	+ +	18 $\frac{1}{12}$	—	15	14–16	—
12	B. G.	XO	—	—	+	—	+	...	...	...	18 $\frac{7}{12}$	—	16	12–13	—
13	K. A.	XO	—	+	+	—	+	+ +	+ +	—	17 $\frac{2}{12}$	—	14	13	—
14	L. L.	XO	Twice	+	+	—	+	+ +	+ +	—	19 $\frac{5}{12}$	—	12–13	—	15
15	I. O.	XO	—	—	—	+	+	+ +	+ + +	+	12 $\frac{0}{12}$	—	15	—	—
16	C. L.	XO	—	+	+	+	...	...	...	...	...	...	...	—	—
17	B. H.	XO	—	—	+ +	—	+	+ +	+ + +	+	17 $\frac{7}{12}$	—	15	—	14
18	I. L.	XO	—	—	+	—	+	+ +	+ +	+	17 $\frac{8}{12}$	—	16	13	—
19	K. S.	XO	—	+	—	—	+	...	...	...	18 $\frac{6}{12}$	—	...	—	—
20	B. L.	XO	—	—	—	—	+	+	+	+	15 $\frac{9}{12}$	—	14–15	—	—
21	D. F.	XO	—	—	+	—	+	+ +	+ +	+	15 $\frac{2}{12}$	17 $\frac{4}{12}$	14	10–11	—
22	I. H.	XO	Once	—	+	—	+	+ +	+ +	—	20 $\frac{9}{12}$	—	17	17	—
23	S. I. H.	XO	—	—	—	—	+	+ +	+ +	—	17 $\frac{0}{12}$	23 $\frac{5}{12}$	11	11	—
24	I. A.	XO	—	—	+	—	+	+ +	+ +	+	—	—	12	11–12	—
25	B. A.	XO	For 7 years	+ +	+ +	+ +	...	...	...	...	—	—	14	12	—
26	B. S-n.	XO	—	—	—	—	+	+	+	+	17 $\frac{3}{12}$	21 $\frac{7}{12}$	14	—	—
27	R. L.	XO	—	+	+	—	+	+ +	+ +	+	21 $\frac{3}{12}$	22 $\frac{7}{12}$	15	—	—
28	V. S.	XO	—	+	+	—	+	+ +	+ + +	—	23 $\frac{5}{12}$	25 $\frac{6}{12}$	11	—	24
29	G. A.	XO	—	—	+	—	+	...	...	...	28 $\frac{2}{12}$	—	12	—	—
30	G. K.	XO	—	—	+ +	—	+	+ +	+ + +	+	20 $\frac{10}{12}$	—	...	12–13	—
31	A. F.	XO	—	—	—	—	+	+	+ +	+	17 $\frac{11}{12}$	26 $\frac{3}{12}$	13–14	—	18
32	M. N.	XO	3 times	+	+	—	+	+ + +	+ +	+	19 $\frac{10}{12}$	28 $\frac{11}{12}$	13–14	—	—
33	M. S. L.	XO	—	—	+	—	+	+ +	+ +	+	17 $\frac{3}{12}$	27 $\frac{8}{12}$	14	11	17
34	V. P.	XO	—	+	+	...	+	+ + +	+ +	+	21 $\frac{6}{12}$	28 $\frac{3}{12}$	13	—	22
35	I. J.	XO	—	+	+	—	...	...	...	...	—	—	13	—	—
36	Y. L.	XX_I	—	+	+	—	...	...	...	...	—	—	12	—	—
37	G. E.	XO/XX_I	—	—	—	—	+	+ + +	+ +	+ +	13 $\frac{2}{12}$	—	14	14	—
38	B. J.	XO/XX_I	—	+	+	+	+	+ +	+ +	+	18 $\frac{0}{12}$	—	14–15	—	—
39	B. S.	XO/XX_I	—	—	—	—	+	...	...	...	18 $\frac{11}{12}$	—	12	13–14	—

Table 20 (*continued*)

Patient			Before oestrogen therapy				After oestrogen therapy				Oestrogen therapy: Age of		Menarche		Age at laparotomy:[e] years
					Growth of				Growth of						
No.	Initials	Sex chromosome constitution	Menstruation[a]	Breast development[b]	Pubic hair[c]	Axillary hair[d]	Menstruation	Breast development[b]	Pubic hair[c]	Axillary hair[d]	Onset, years	Withdrawal, years	Mother	Sisters	
40	A. S.	XO/XX_I	—	—	—	—	+	+ +	+ +	+	14 10/12	—	15	14	17
41	L. A.	XO/XX_I	—	—	—	—	+	—	—	—	17 5/12	18 3/12	15	—	18
42	C. S.	XO/XX_I	—	—	+	+	+	+	+ +	+	15 1/12	—	13–14	11–12	16
43	E. S.	$XO/XX_I/XX_I X_I$	—	—	—	—	+	+ +	+	+	14 11/12	~20	15	—	—
44	M. A.	XX_I	—	+	+	—	+	+ +	+ +	—	18 3/12	24 5/12	17	13	—
45	M. J.	XO/XX_I	—	+	—	—	+	+	+ +	+	16 6/12	~20	16–17	14–15	—
46	R. K.	XO/XX_I	—	+	+	+	+	+ +	+ + +	+ +	19 11/12	23 2/12	14	—	19
47	M. C.	XO/XX	—	—	+ +	+	+	...	...	...	17 11/12	—	14	12	17
48	S. S.	XO/XX	—	—	—	—	+	+ +	+	+	13 5/12	14 2/12	...	—	15
49	B. N.	XO/XX	—	—	+ +	+	+	+	+ +	+	18 5/12	—	13	14	—
50	A. H.	XO/XX	—	+	+ +	+	+	+ +	+ +	+ +	17 5/12	17 11/12	15	—	—
51	M. H.	XO/XX	4 times	+ + +	+ + +	+ +	+	+ + +	+ + +	+ +	16 7/12	—	12–13	12–13	—
52	E. K.	XO/XX	—	+ + +	+ + +	+ +	+	+ + +	+ + +	+ +	32 10/12	—	15–16	14–15	25
53	S. Ö.	XO/XX	For 16 years	+ +	+ +	+	+	+ +	+ +	+	32 4/12	—	...	...	—
54	E. H.	XX	For 6 years	+ + +	+ + +	+ +	...	...	...	...	—	—	11	13–14	—
55	G. S.	$XO/XX_R/XX_R X_R$	For 7 years	+ + +	+ + +	+ +	+	+ + +	+ + +	+ +	20 7/12	21 5/12	...	—	22
56	I. P.	XO/XX_D	—	+	+	—	+	+ +	+ + +	+	14 6/12	—	13–14	—	—
57	E. B. H.	XO/?	For 1 year	...	...	—	+	+ +	+ +	—	16 7/12	17 8/12	11	12–13	16

[a] When menstruation occurred it was usually irregular and infrequent

[b] – – = no development at all, infantile.
+ = slight lipomastia and/or minor developmental changes in the nipples, but no glandular tissue palpable.
+ + = hypoplastic breasts, palpable glandular tissue and moderate development of the nipples.
+ + + = within normal limits.

[c] – = none. + = very scanty. + + = moderate, but less than normal. + + + = within normal limits.

[d] – = none. + = moderate, but less than normal. + + = within normal limits.

[e] The findings at laparotomy are described in the Case reports.

Fig. 13. (*a*) Case 2 at the age of one month.
(*b*) Feet of Case 2 at the age of one month. Note bilateral oedema.
(*c*) Left foot of Case 2 at the last examination, at seven and a half months. Note oedema.

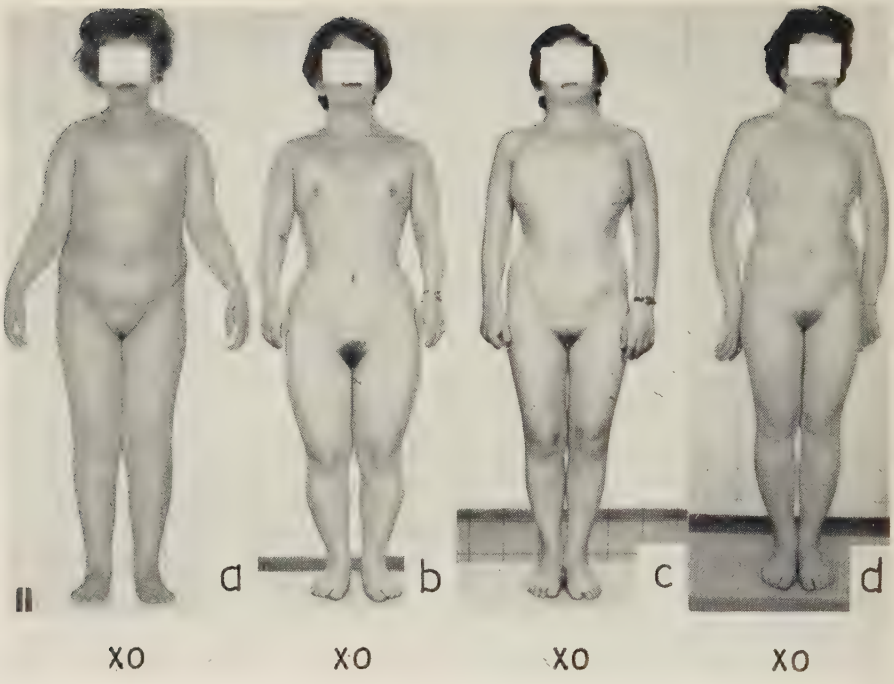


Fig. 14. Four patients with an XO sex chromosome constitution.

(*a*) Case 7 at the age of 17 years. Height 147 cm. Before oestrogen treatment. Note cubitus valgus.

(*b*) Case 15 at the age of 19 years. Height 141 cm. Treated with oestrogens between 12 and 19 years of age.

(*c*) Case 23 at the age of 24 years. Height 149 cm. Treated with oestrogens between 17 and 23 years of age.

(*d*) Case 27 at the age of 26 years. Height 155 cm. Treated with oestrogens between 21 and 22 years of age.

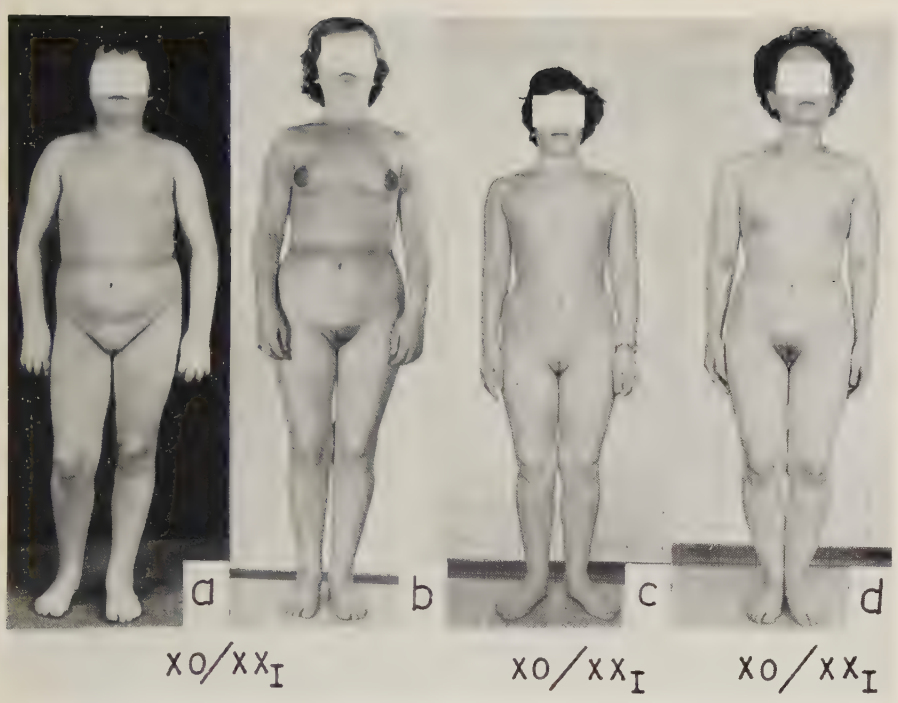


Fig. 15. Three patients with an XO/XX$_I$ sex chromosome constitution.
(*a*) Case 37 at the age of 14 years. Height 134 cm. Before oestrogen treatment.
(*b*) Case 37 at the age of 17 years and after three years of oestrogen administration. Height 142 cm.
(*c*) Case 39 at the age of 19 years. Height 139 cm. Before oestrogen treatment.
(*d*) Case 46 at the age of 30 years. Height 134 cm. Treated with oestrogens between 20 and 23 years of age.

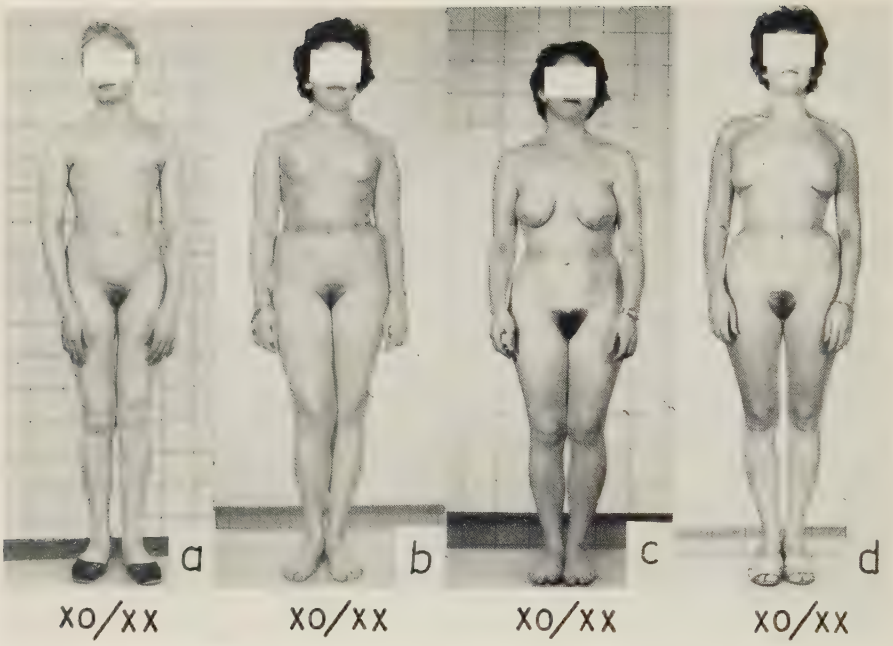


Fig. 16. Four patients with an XO/XX sex chromosomè constitution.

(*a*) Case 49 at the age of 18 years. Height 152 cm. Before oestrogen treatment.

(*b*) Case 50 at the age of 20 years. Height 154 cm. Treated with oestrogens for half a year at the age of 17 years.

(*c*) Case 51 at the age of 23 years. Height 148 cm. Treated with oestrogens from 16 years of age.

(*d*) Case 52 at the age of 33 years. Height 153 cm. Before oestrogen treatment. Note normal pubic hair growth and breast development.

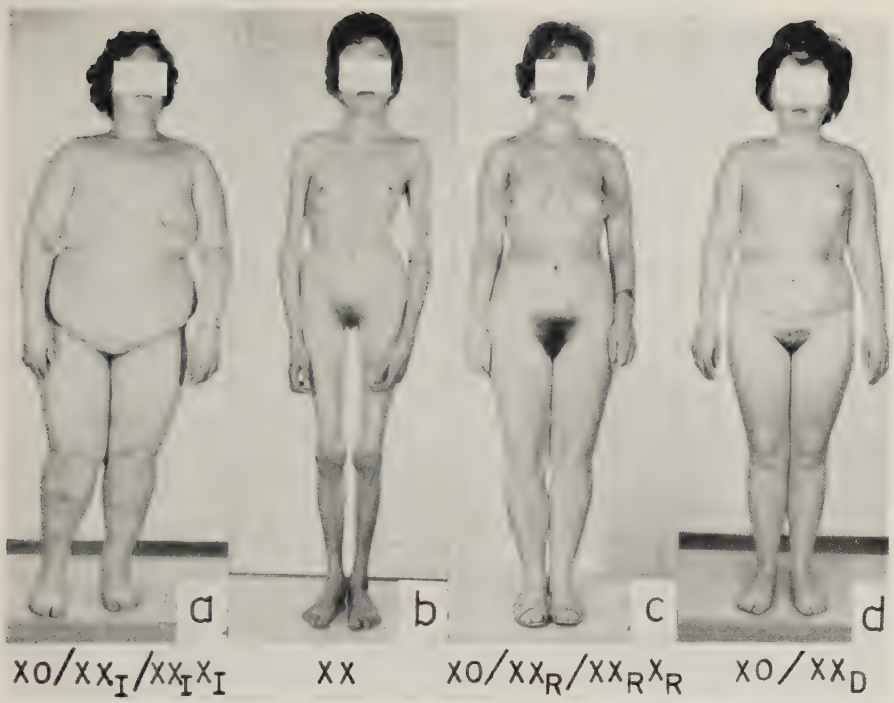


Fig. 17. Four patients with various sex chromosome constitutions.

(*a*) Case 43 at the age of 24 years. Height 149 cm. Treated with oestrogens between 15 and 20 years of age. XO/XX$_I$/XX$_I$X$_I$.

(*b*) Case 54 at the age of 19 years. Height 142 cm. Not treated with oestrogens. XX.

(*c*) Case 55 at the age of 22 years. Height 143 cm. Treated with oestrogens between 21 and 22 years of age. Note normal pubic hair growth and breast development. XO/XX$_R$. XX$_R$X$_R$.

(*d*) Case 56 at the age of 22 years. Height 137 cm. Treated with oestrogens from 14 years of age. XO/XX$_D$.

Fig. 18. Some common malformations of the head and neck.

(*a*) Case 24 at the age of 24 years. Note the great number of pigmented naevi.

(*b*) Case 30 at the age of 29 years. Note webbing of the neck and ptosis of the right eye-lid.

(*c*) Case 54 at the age of 18 years. Note webbing of the neck, hypertelorism and bilateral ptosis.

(*d*) Cases 5 at the age of 16 years. Note epicanthic folds.

(*e*) Case 11 at the age of 18 years. Note epicanthic folds.

(*f*) Case 27 at the age of 21 years. Note low implantation of hair.

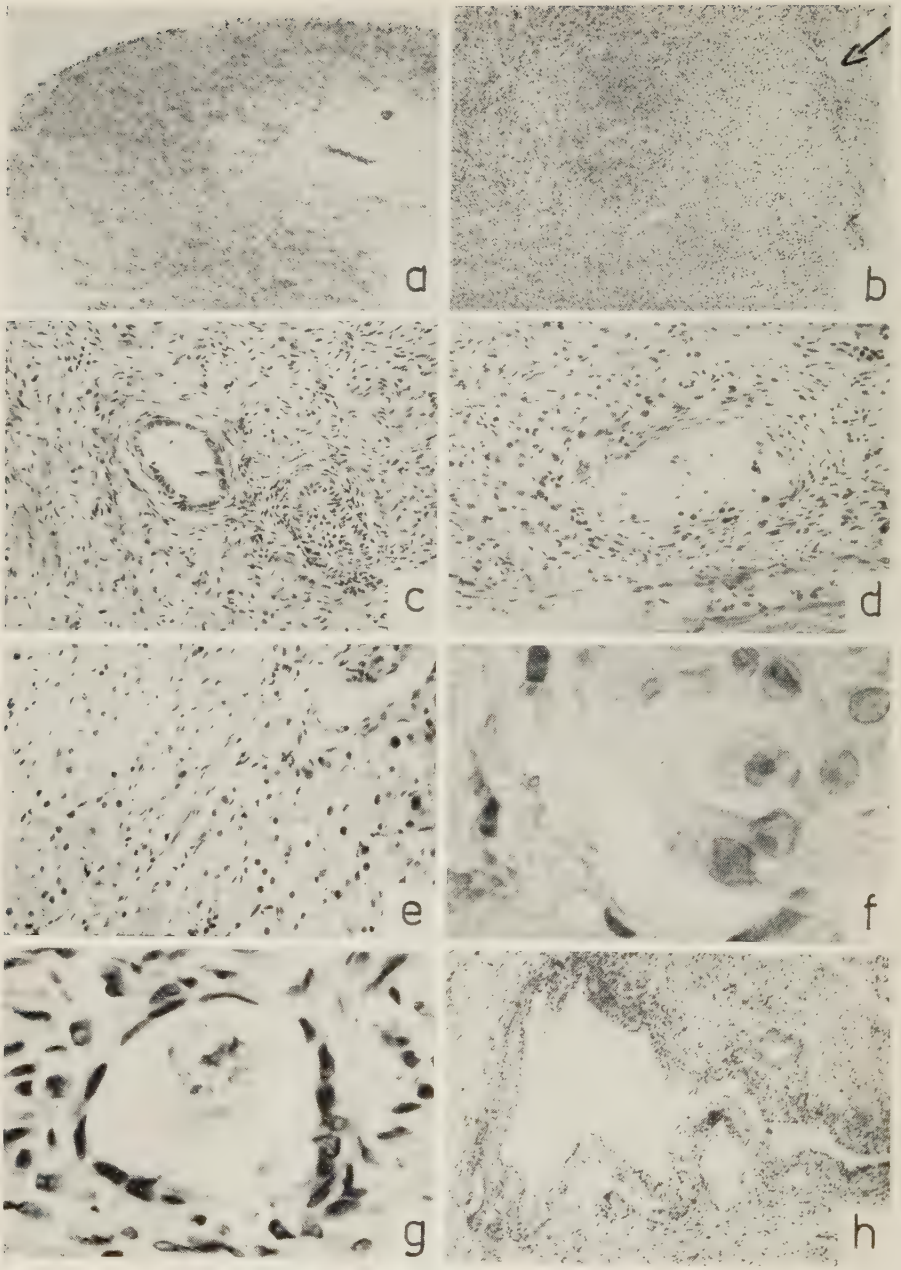
Fig. 19. Some malformations of the hands and feet.

(*a*) Feet of Case 5 at the age of 16 years. Note persisting oedema of the right foot.

(*b*) Feet of Case 8 at the age of 17 years. Note bilateral malformation of the fourth toe. This was mainly due to short fourth metatarsal bones.

(*c*) Feet of Case 24 at the age of 23 years. Note the hypoplastic nails and the short fourth toe on the left foot. This was mainly due to a short, fourth metatarsal bone.

(*d*) Hands of Case 18 at the age of 21 years. Note the short fourth and fifth fingers on both sides, mainly due to short fourth and fifth metacarpal bones.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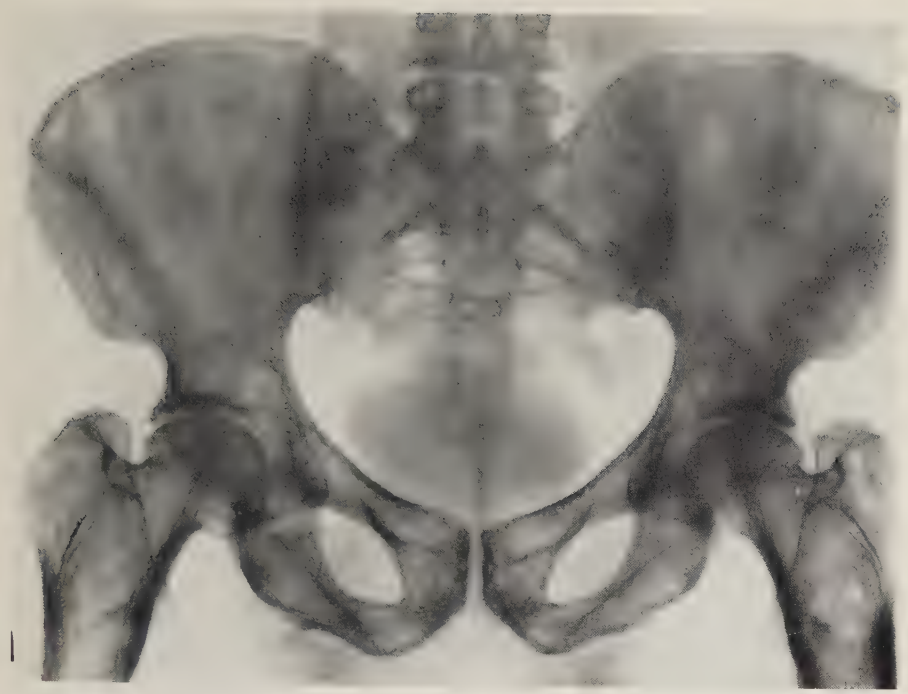


Fig. 21. Case 35. Pronounced dysplastic skeletal structure of the pelvis, sacrum and proximal femur.

Fig. 20. Microphotographs of "gonadal" tissue stained with van Gieson.

(*a*) Case 7. Cross-section of a "streak" gonad. Connective tissue arranged in whirls as in normal ovarian stroma. No visible follicles or corpora lutea. × 57.

(*b*) Case 42. Ectopic adrenal cortex found in the left "streak" gonad. Note the typical structure of zona fasciculata to the right. The arrow indicates a thin capsule, outside which cells of the type found in the hilar region of normal ovaries ("hilar cells", "hilar Leydig cells") are seen. × 40.

(*c*) Case 7. Remnants of mesonephric ducts found in the inner layer of the connective tissue of the "streak" gonads. × 150.

(*d*) Case 7. Remnant of a mesonephric tubule very similar to an immature testicular tubule. × 210.

(*e*) Case 7. Cluster of "hilar cells". × 190.

(*f*) Case 42. Higher magnification of some of the cells in a cluster of "hilar cells". Crystalloids of the Reinke type of testicular Leydig cells are seen. × 820.

(*g*) Case 55. Primordial follicle with ovum. × 1500.

(*h*) Case 55. Part of a follicular cyst, damaged during preparation. × 72.

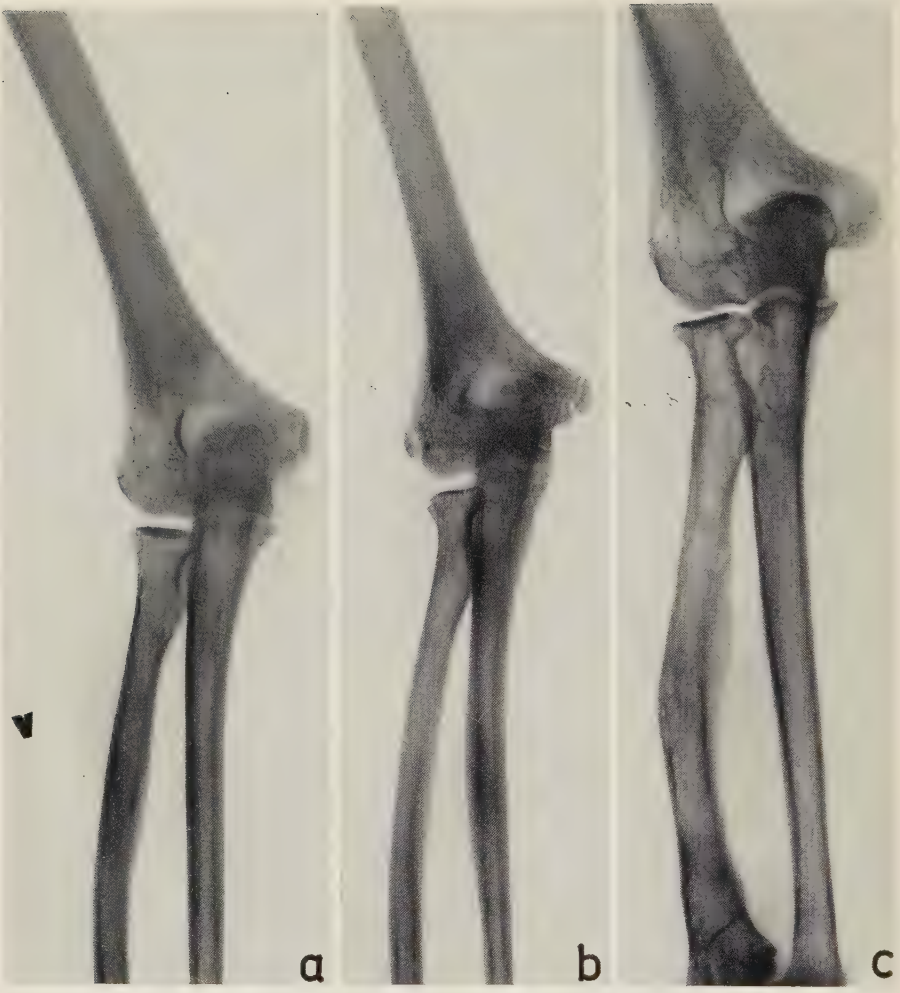
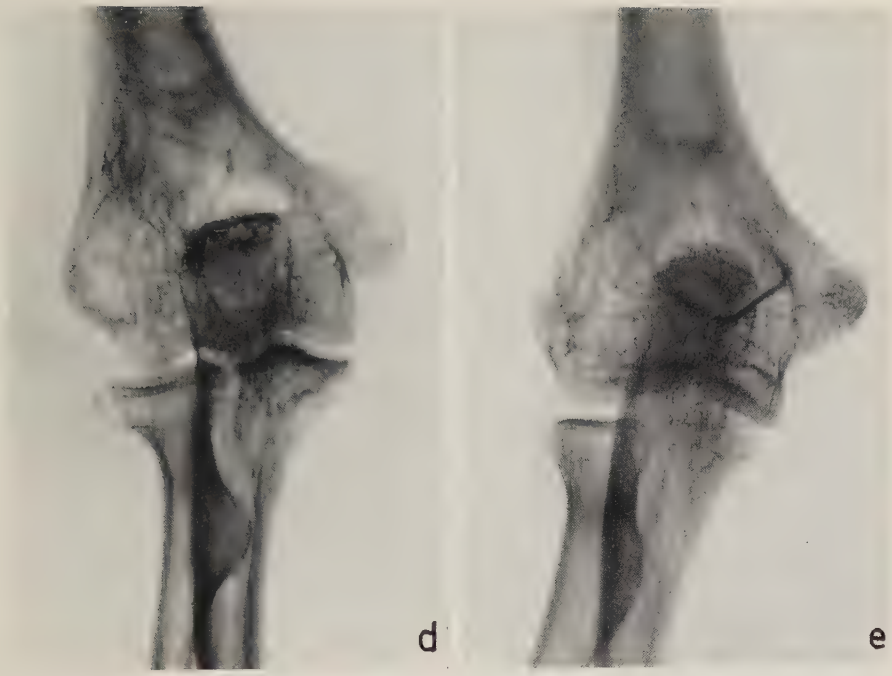


Fig. 22. (*a*) Case 36. True cubitus valgus with underdevelopment, especially of the capitulum humeri, no extension defect.
(*b*) Case 6. Slight cubitus valgus caused by an extension defect.
(*c*) Case 35. Slight deformation of the elbow joint and pronounced dysplastic skeletal structure. The radius is short and S-shaped.



(*d*) Case 21. Slight deformation of the elbow joint with increased width of the capitulum radii and slightly dysplastic skeletal structure.
(*e*) Case 42. Underdevelopment of the capitulum and trochlea humeri and slightly dysplastic skeletal structure.

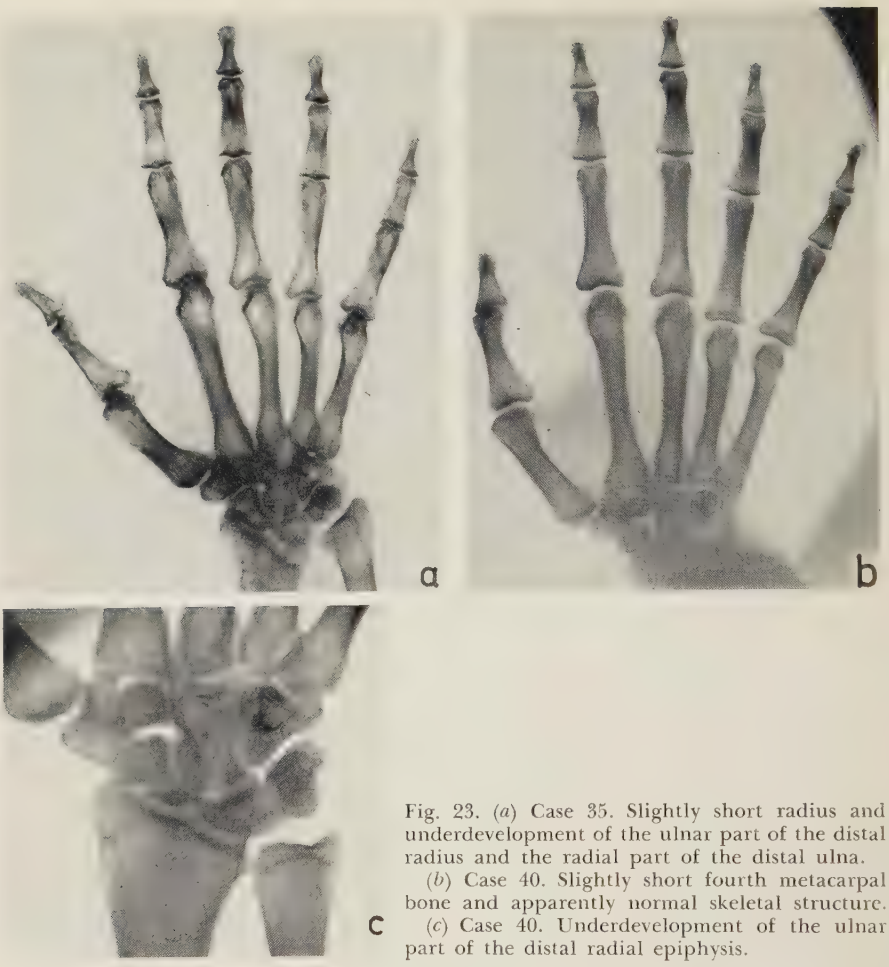


Fig. 23. (*a*) Case 35. Slightly short radius and underdevelopment of the ulnar part of the distal radius and the radial part of the distal ulna.
(*b*) Case 40. Slightly short fourth metacarpal bone and apparently normal skeletal structure.
(*c*) Case 40. Underdevelopment of the ulnar part of the distal radial epiphysis.

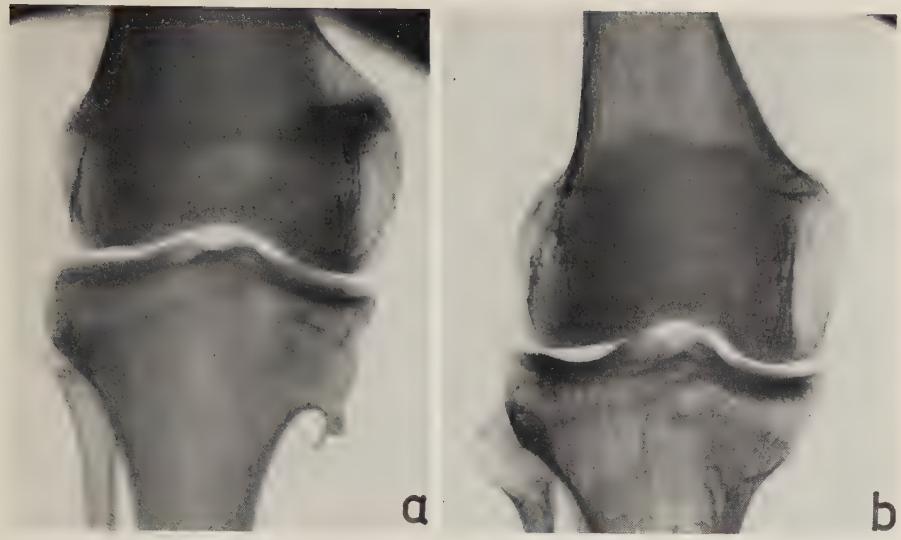


Fig. 24. (*a*) Case 48. Skeletal deformation of the knee joint (see *Kosowicz* 1959) often found in patients with Turner's syndrome.
(*b*) Case 30. Slight genu varus due to the deformation of the proximal tibia.

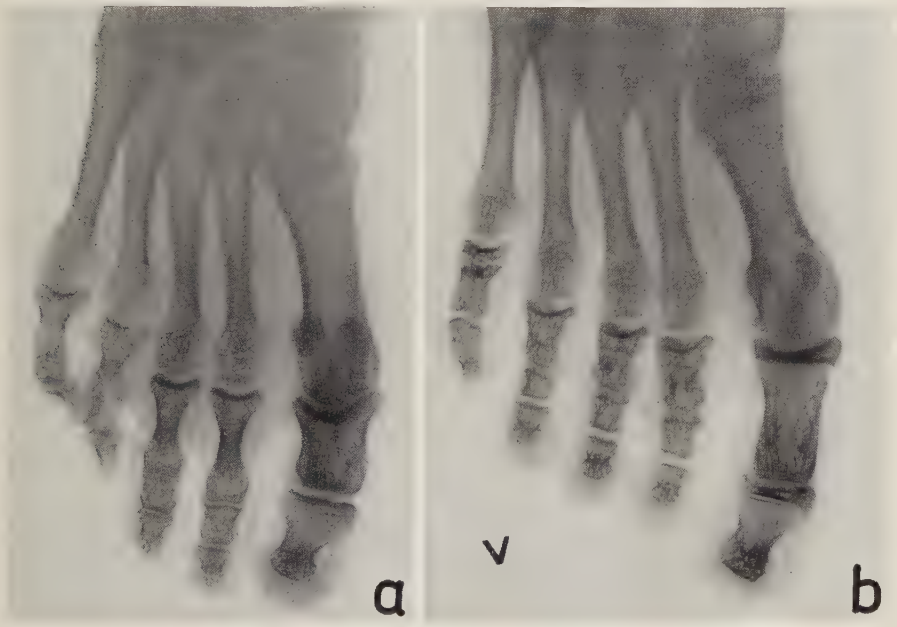


Fig. 25. (*a*) Case 37. Slightly short fourth metatarsal bone and slight underdevelopment of the proximal phalanx of the first toe.
(*b*) Case 39. Underdeveloped proximal phalanges on the second, third and fourth toes. Dysplastic skeletal structure.

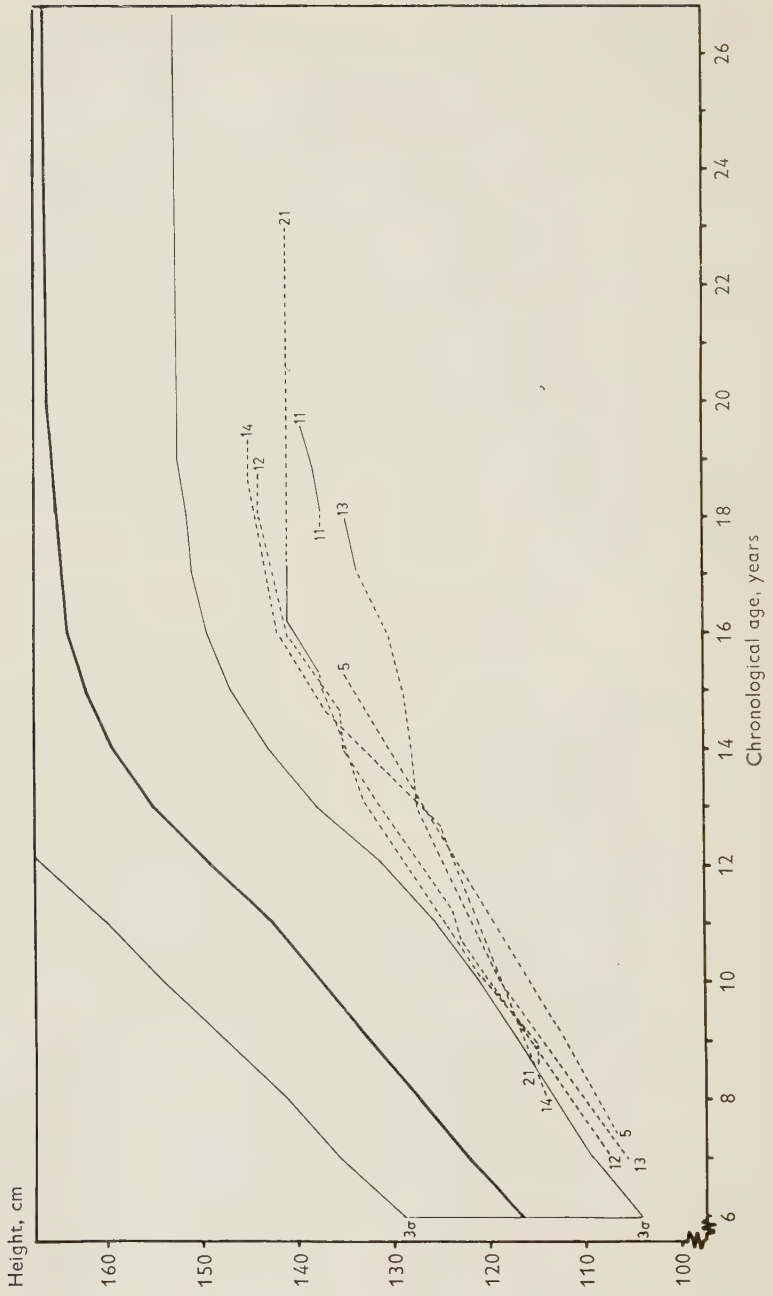
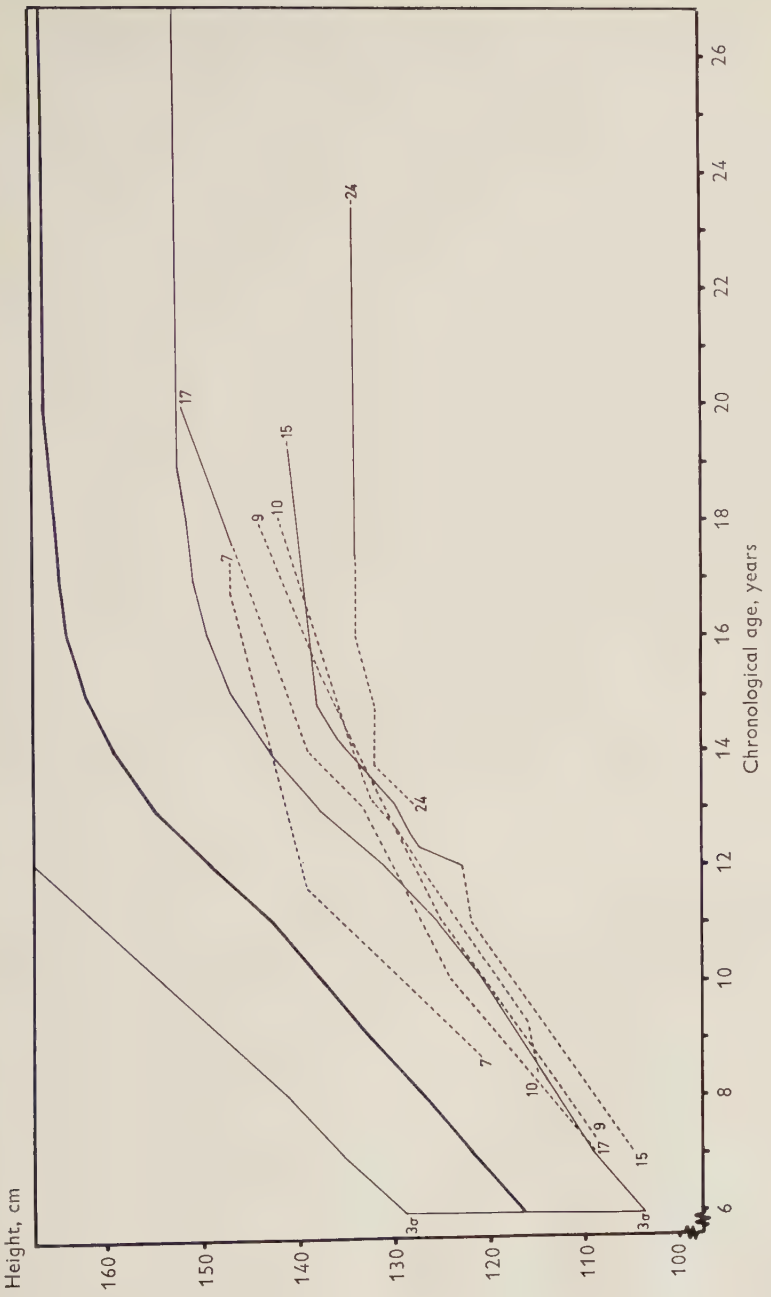


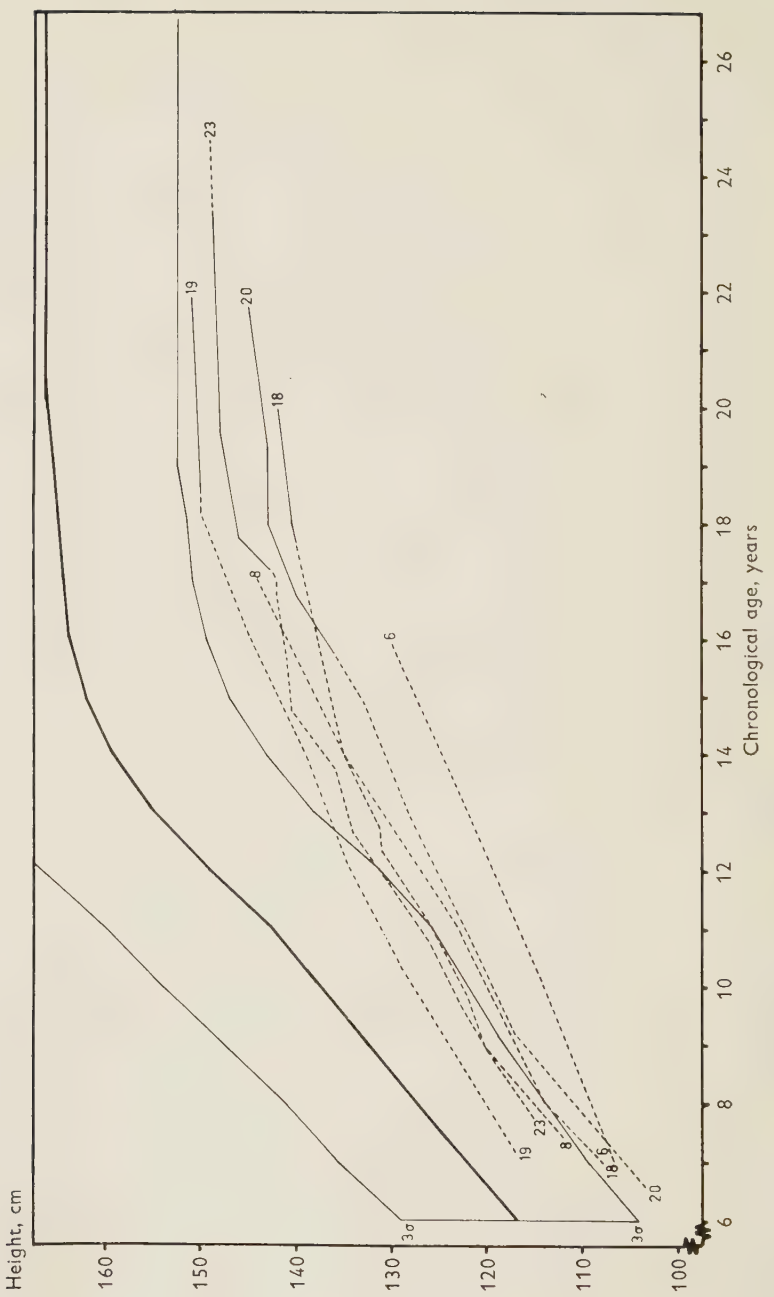
Fig. 26. Growth curves for individual patients. The case number is found at the beginning and at the end of each curve. During the time the patient was treated with oestrogens the lines are unbroken, otherwise they are dotted.

Curves of the mean height and 3σ limits for normal Swedish females are also given.

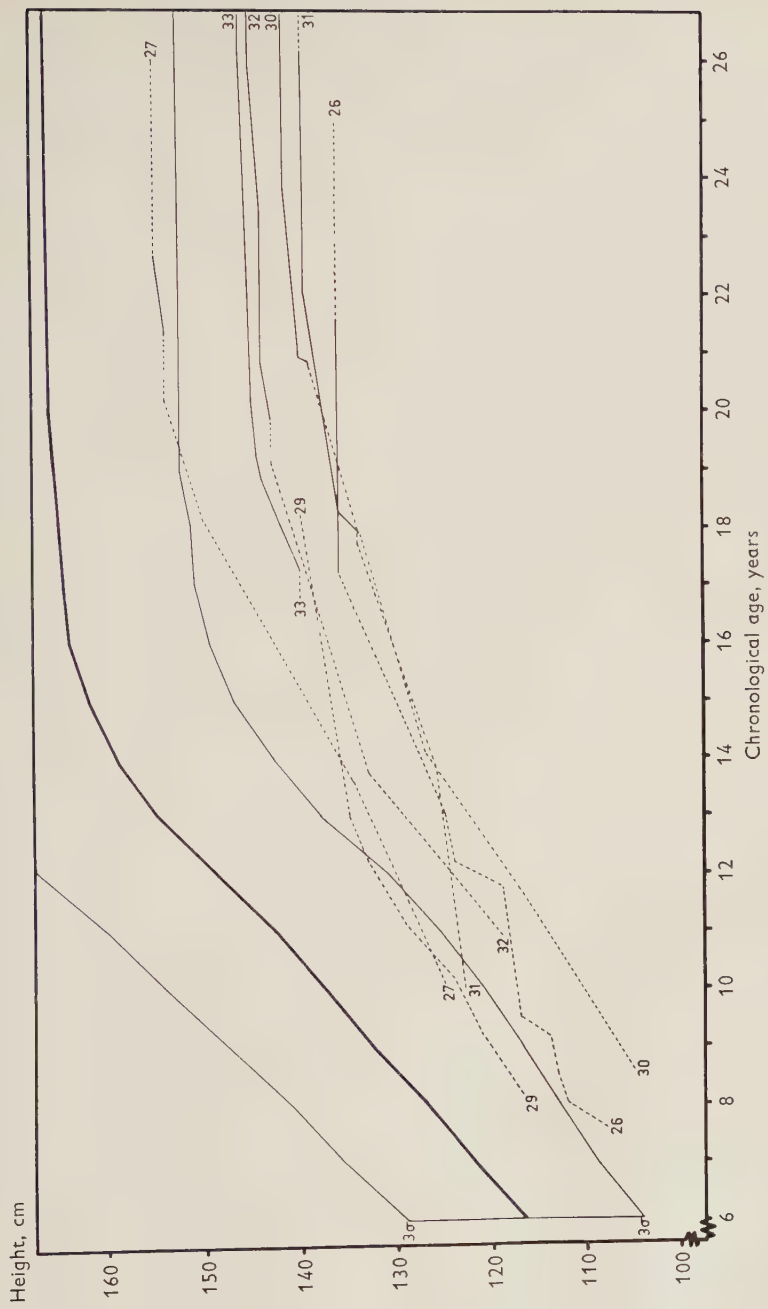
(*a*) Six cases with an XO sex chromosome constitution.



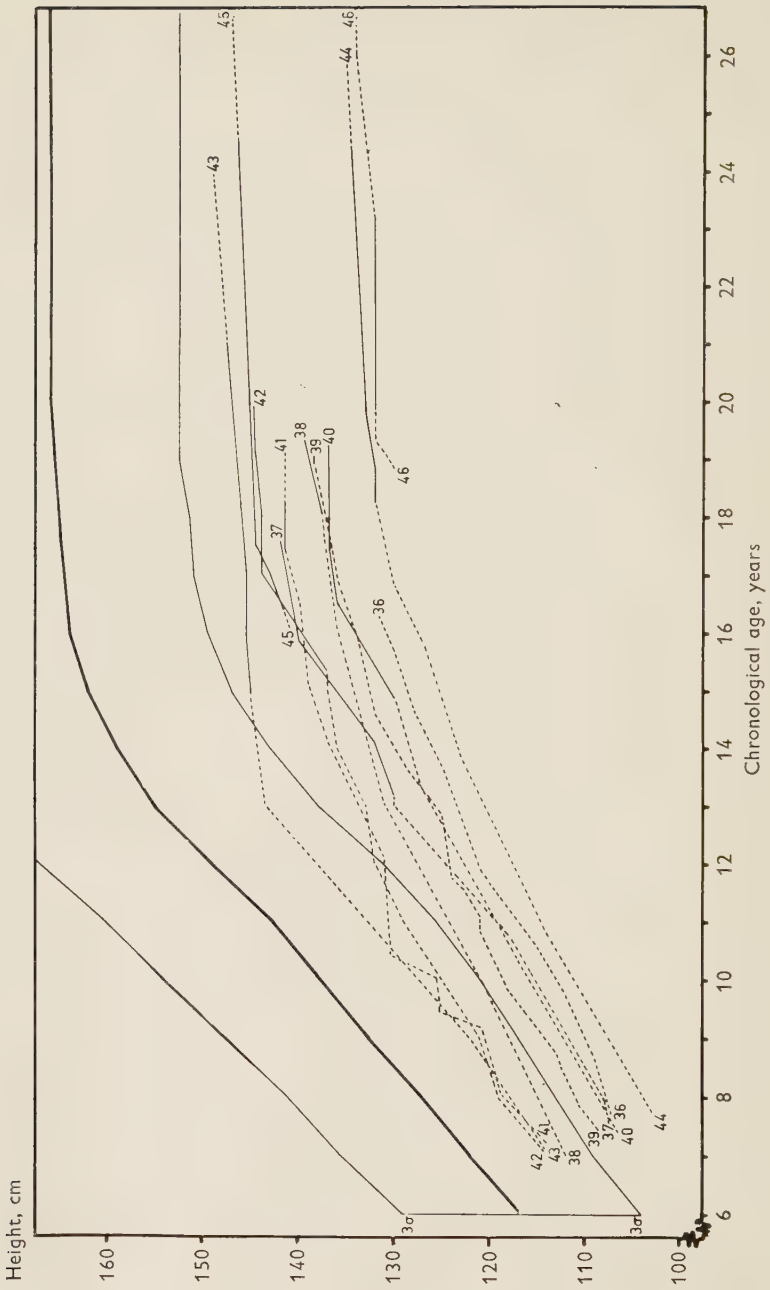
(*b*) Six cases with an XO sex chromosome constitution.



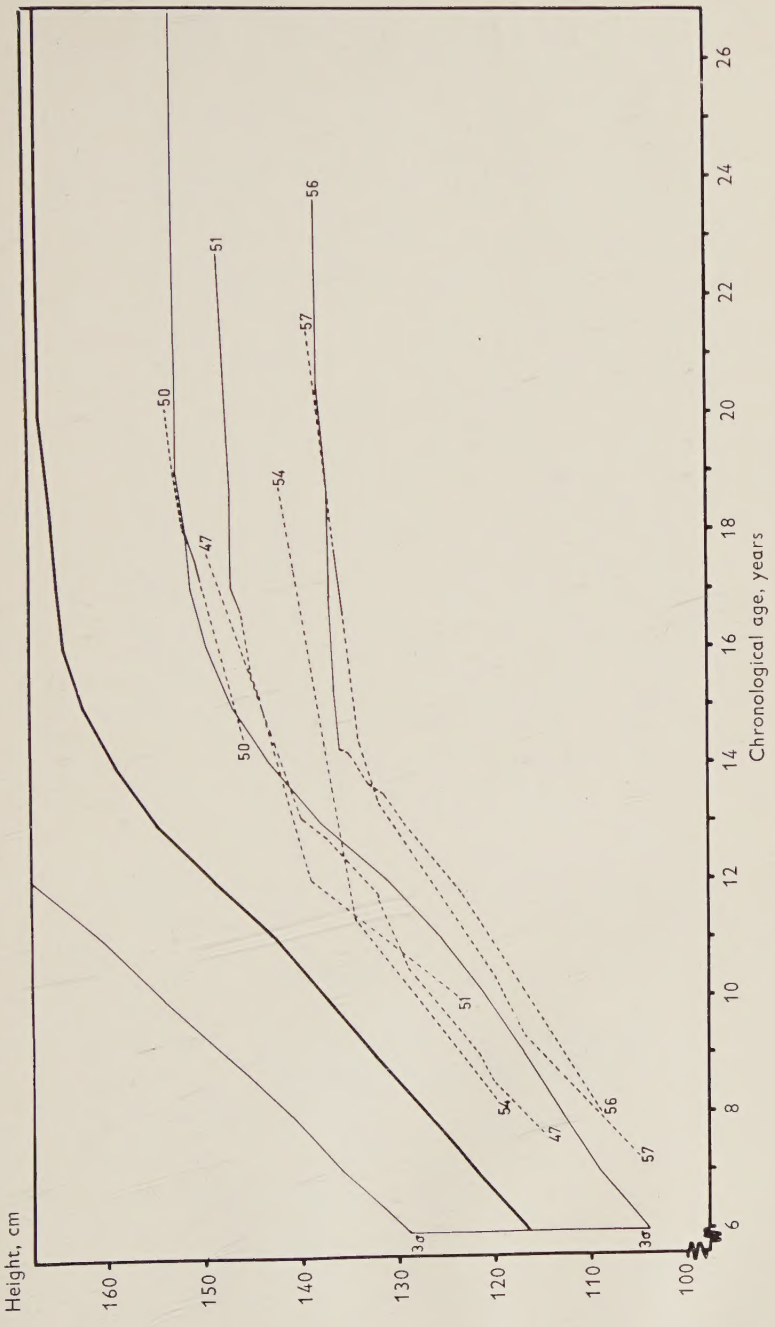
(*c*) Six cases with an XO sex chromosome constitution.



(*d*) Seven cases with an XO sex chromosome constitution.



(*e*) Eleven cases with presumptive iso-chromosomes for the long arm of X, with or without mosaicism.



(*f*) Six cases with various types of sex chromosome constitution: XO/XX, XX, XO/XX_D, XO/?.

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